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Deciphering breast cancer cell heterogeneity: a quantum dot-conjugate approach employing MCF-7 and THP-1 co-cultures†

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This study developed and utilized quantum dot conjugates labeled with antibodies ($QD^{\lambda/Ab}$) to analyze the heterogeneity of cancer cell populations in co-cultured MCF-7/THP-1 cells mimicking peripheral blood conditions. We synthesized QD^{λ} with emissions at 450 nm, 525 nm, and 615 nm, confirmed by transmission electron microscopy and X-ray diffraction analysis, suggesting distinct crystal structures and phase transitions. Surface modification with β-mercaptopropionic acid ($QD^{\lambda/MPAb}$), polyethylene glycol ($QD^{\lambda/MPA/PEG}$) and streptavidin ($QD^{\lambda/MPA/PEG/SA}$) enhanced biocompatibility and enabled specific antibody binding, as evidenced by consistent fluorescence and dynamic light scattering analysis. Flow cytometry and confocal microscopy validated the selective binding of antibodies to cancer markers and revealed significant heterogeneity within the cell populations. This study underscores the potential of $QD^{\lambda/Ab}$ conjugates for precise cancer biomarker detection and heterogeneity assessment.

Introduction

Globally, breast cancer continues to be the primary cause of cancer-related deaths in women.[1,2] The transition from a pre-cancerous state to invasive carcinoma is called metastasis, which causes the subsequent spread of cancer cells to other parts of the body, posing significant challenges in clinical practice.[3,4] The disease exhibits a range of histopathological characteristics, including variations in receptor activities, such as the estrogen receptor, progesterone receptor, and ERBB2/HER2.[5–7] These receptor activities are important for diagnosing the disease, conducting molecular profiling, and determining clinical prognosis and therapeutic response.[8,9] The landscape of breast cancer has become more complex due to the recent developments in genomic and transcriptome analysis, which have identified additional subgroups with diverse clinical outcomes.[10,11] The presence of diverse cancer cell types inside the tumour microenvironment, known as cancer cell heterogeneity (CCH), greatly impacts the complexity of cancer treatment.[12,13] The variability of cells observed in tissues, either healthy or malignant forms, can be attributed to genetic differences or cell-level plasticity.[14,15] Determining the variation in the tumour structure has always been crucial in the advancement of tumour grading and prognostic classification systems. This variation affects the proliferation of tumour cells, the infiltration of the immune system, and the differentiation states of the tumour, among other factors.[16–18]

The significance of cellular heterogeneity in metastasis and disease progression has been established by many researchers, although identifying and characterizing this diversity remains a formidable task in the present biomedical research.[19–22] Tumour development, dissemination, and response to therapy are highly dynamic processes that can vary greatly within intra-tumor heterogeneity and inter-tumor heterogeneity.[23–26] This variability contributes to the complexity of comprehending and managing tumours. Therefore, it is crucial to have precise biomarkers and novel methods to accurately identify and analyse CCH to advance cancer diagnosis and therapy.

This study builds upon our previous work (Vyshnava *et al.*, 2022) and aims to overcome the current challenges associated with cellular heterogeneity in breast cancer by employing

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quantum dot antibody conjugates ($QD^{\lambda/Ab}$, where λ is the emission wavelength and Ab is the conjugated antibody) to investigate the diversity of cancer cells in *in vitro* co-cultures of MCF-7 and THP-1 cell line systems.[27] Our objective is to highlight the intricacies of CCH, its impact on the spread of cancer, and the consequences for patients by examining markers such as EpCAM (epithelial cellular adhesion molecule), CD44 (cell-surface glycoprotein), and CD45 (protein tyrosine phosphatase). This work expands on the existing understanding of the relationships between the tumour microenvironment and cancer cell plasticity, providing valuable insights into possible diagnostic and therapeutic approaches.

Results and discussion

This study employed $QD^{\lambda/Ab}$ conjugates to investigate the heterogeneity of a cancer cell system of MCF-7/THP-1 co-cultures, which mimic peripheral blood in *in vitro* settings. We have effectively synthesized different types of QD^{λ} with specific emission fluorescence at different wavelengths, where QD^{450} emits blue light at 450 nm, QD^{525} emits green light at 525 nm, and QD^{615} emits red light at 615 nm under excitation from a 405 nm laser, as shown in Fig. 1. Transmission electron microscopy (TEM) analysis showed distinct crystals with diameters of 3.40 ± 0.06 nm for QD^{450} (*d*-spacing of 17 Å), 4.00 ± 0.40 nm for QD^{525} (*d*-spacing of 30 Å), and 5.30 ± 0.90 nm for QD^{615} (*d*-spacing of 33 Å), which are consistent with previously published research studies.[28–30] X-ray diffraction (XRD) analysis provided additional confirmation of the crystal structures of these QD^{λ}. The presence of prominent peaks corresponding to lattice indices (100), (002), (101), (102), and (110) indicated that QD^{450} likely possesses a zinc blende or wurtzite structure, as shown in Fig. 1a. On the other hand, QD^{525} and QD^{615} exhibited transitions from hexagonal to cubic phases, which was evidenced by the presence of indices (002), (102), (110), (200), and (202), as shown in Fig. 1b and c, and these results are consistent with earlier reports.[27,31,32] The results suggest that the core–shell QD^{λ} that were synthesized are highly crystalline and exhibit intense emission intensities (refer to ESI,† Table S1).

The QD^{λ}'s biocompatibility was improved through surface modifications utilizing β-mercaptopropionic acid (MPA) and carboxy amine polyethylene glycol (PEG). This was achieved by exchanging ligands ($QD^{\lambda/MPA}$), resulting in the QDs acquiring a negative charge ($-COO^-$) and coupling reaction with EDC/NHS to bind the PEG ($QD^{\lambda/MPA/PEG}$) (refer to the Methodology section of the ESI†). The existence of functional groups such as –COOH (1490 cm^{-1}), $-NH_2$ (1635 cm^{-1}), and –OH (3348 cm^{-1}), which indicate the stability and compatibility of the modified QDs, was confirmed using Fourier-transform infrared (FTIR) spectroscopy (refer to ESI,† Fig. S1a and b), and correlated with earlier reports.[33–35] Additional optical investigations revealed that the modified $QD^{\lambda/MPA}$ and $QD^{\lambda/MPA/PEG}$ exhibited consistent fluorescence emissions, albeit with lower quantum yields compared to the original core/shell QD^{λ} (refer to ESI,† Fig. S2 and Table S2). To simplify the process of binding antibodies (Abs), we utilized a streptavidin–biotin linkage. The successful binding of biotin-tagged Abs, which include the anti-EpCAM, anti-CD45 and anti-CD44 to the streptavidin-conjugated quantum dots ($QD^{\lambda/MPA/PEG/SA}$), was verified by observing consistent fluorescence emissions in the optical analyses, as shown in Fig. 2 (for convenience, the Abs tagged to $QD^{\lambda/MPA/PEG/SA/Ab}$ is represented as $QD^{\lambda/Ab}$ such as $QD^{450/EpCAM}$, $QD^{525/CD45}$ and $QD^{615/CD44}$), which are consistent with earlier reports.[36,37] Dynamic light scattering (DLS) data in Fig. S1 and S2 (ESI†) further support these findings, confirming previous investigations.[38]

Before performing the studies with the cell lines, the modified QDs (which include $QD^{\lambda/MPA}$ and $QD^{\lambda/MPA/PEG}$) were tested for cytotoxicity with the respective cell lines including MCF-7 and THP-1. Here, we observed that the $QD^{\lambda/MPA}$ showed relative cytotoxicity in the concentration range of 20–40 μg mL^{-1} compared to $QD^{\lambda/MPA/PEG}$, which showed toxicity at ~40 μg mL^{-1} for all three QD^{λ}'s (ESI,† Fig. S3). The IC_{50} value for $QD^{\lambda/MPA}$ and $QD^{\lambda/MPA/PEG}$ is ~80 μg mL^{-1}, while it was ~100 μg mL^{-1} for the other two. These observations showed that the modified $QD^{\lambda/MPA/PEG}$ is more convenient and biocompatible for cellular applications than $QD^{\lambda/MPA}$. These observations are in line with the earlier studies of QD^{λ} modifications for bio-applications.[39,40]

Later, we conducted a series of methods to determine and comprehend the heterogeneous characteristics of the cancer cell microenvironment. The primary emphasis was on the optimization, calibration, and analysis of the heterogeneity in the co-cultures. At first, we optimized the efficiency of the $QD^{\lambda/Ab}$ conjugates through the control experiments, where the untreated cell lines were analysed using flow cytometry. The results shown in Fig. S4 (ESI†) indicated that there was an absence of fluorescence within the anticipated gates of the flow cytometry dot plots. This demonstrated the absence of autofluorescence that might potentially interfere with the study. The optimization method validated the selectivity of $QD^{\lambda/Ab}$ conjugates for the MCF-7 and THP-1 cell lines, as illustrated in Tables S3 and S4 (ESI†). When these cells were treated with the corresponding $QD^{\lambda/Ab}$, the flow cytometry dot plots showed unique signal distributions with the respective gates.

Specifically, blue ($QD^{\lambda/EpCAM}$), and red ($QD^{\lambda/CD44}$) emissions were detected, confirming the presence of the antigens EpCAM and CD44 in the sMCF-7 cells, and green ($QD^{\lambda/CD45}$) emissions for CD45 in the THP-1 cells, which are depicted in Fig. 3. The phenotypes were confirmed using confocal microscopy, where the sorted cells displayed the anticipated fluorescence patterns. The long-term validity of these results was emphasized by the mean fluorescence intensity (MFI) measurements, which confirmed the selectivity of $QD^{\lambda/Ab}$ for the respective cell lines. Previous studies have associated CD45+ cells to a mesenchymal origin[41,42] and EpCAM+/CD44+[43–45] subpopulations of cells to an epithelial origin, which is consistent with our findings from the optimization phase. Based on these confirmed findings, we proceeded to calibrate our $QD^{\lambda/Ab}$ in a co-cultured system of MCF-7 and THP-1 cells. The cells were incubated overnight using co-culture methods, outlined in the ESI† Methodology section. Conducting this step was crucial to thoroughly evaluate the practicality and precision of the $QD^{\lambda/Ab}$ in a diverse cellular setting.

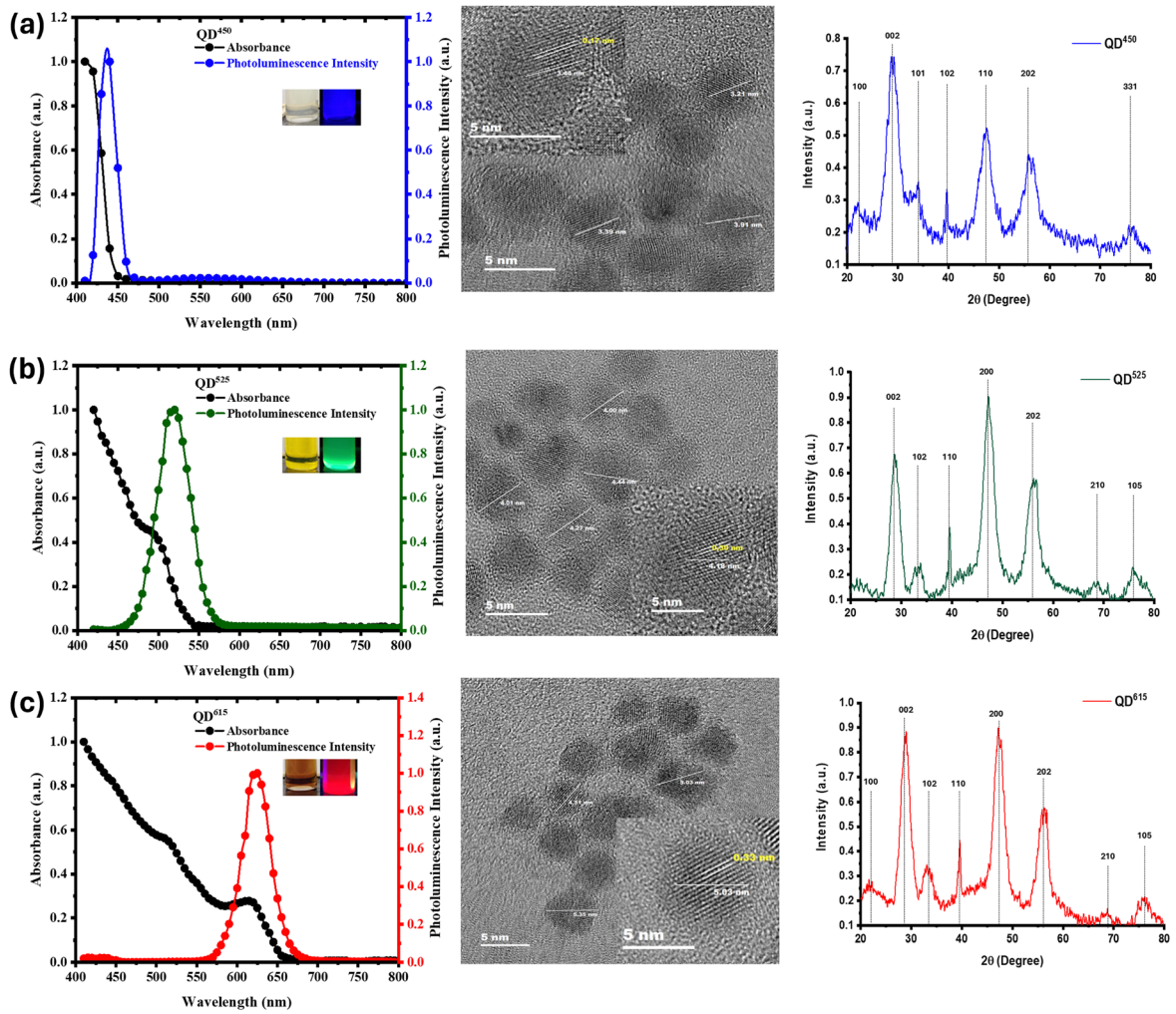

Fig. 1 Morphological characterizations of the core/shell QD$^{\lambda}$ include the UV-visible absorption and fluorescence spectra, high-resolution transmission electron microscopy and X-ray diffraction spectra of (a) QD^{450}, (b) QD^{525}, and (c) QD^{615}. The insets show the bright fluorescence of QD$^{\lambda}$ dots in *n*-hexane solution, including blue, green, and red fluorescence.

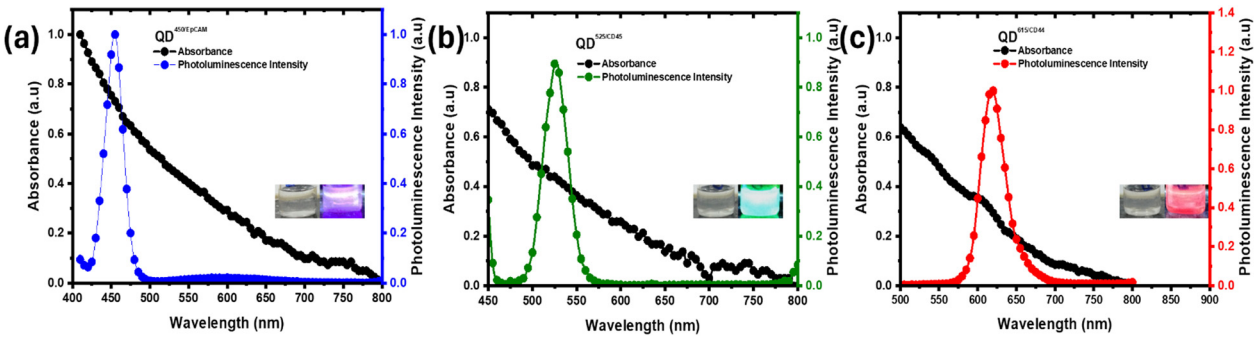

Fig. 2 UV-visible absorption and fluorescence spectra of the QD$^{\lambda}$ with streptavidin (QD$^{\lambda/MPA/PEG/SA}$) modification in 1× PBS buffer at pH 7. The QDs that are added with biotinylated antibodies include (a) QD$^{450/EpCAM}$, (b) QD$^{525/CD45}$, and (c) QD$^{615/CD44}$.

Based on the above observations, QD$^{\lambda/Ab}$ were administered to co-cultured cells at IC_{50} concentrations (40 μg mL^{-1}), with the experimental parameters detailed in Table 1. Analysis of the co-cultured cells revealed effective sorting into defined flow cytometry gates based on specific QD$^{\lambda/Ab}$ bindings. Notably, cells exhibiting bright blue fluorescence were sorted as EpCAM+ (1.83% of cells), those with bright red fluorescence as CD44+ (0.11% of cells), and those with bright green fluorescence as CD45+ (0.42% of cells). Additionally, cell subpopulations were identified with co-expressing EpCAM+/CD45+, EpCAM+/CD44+,

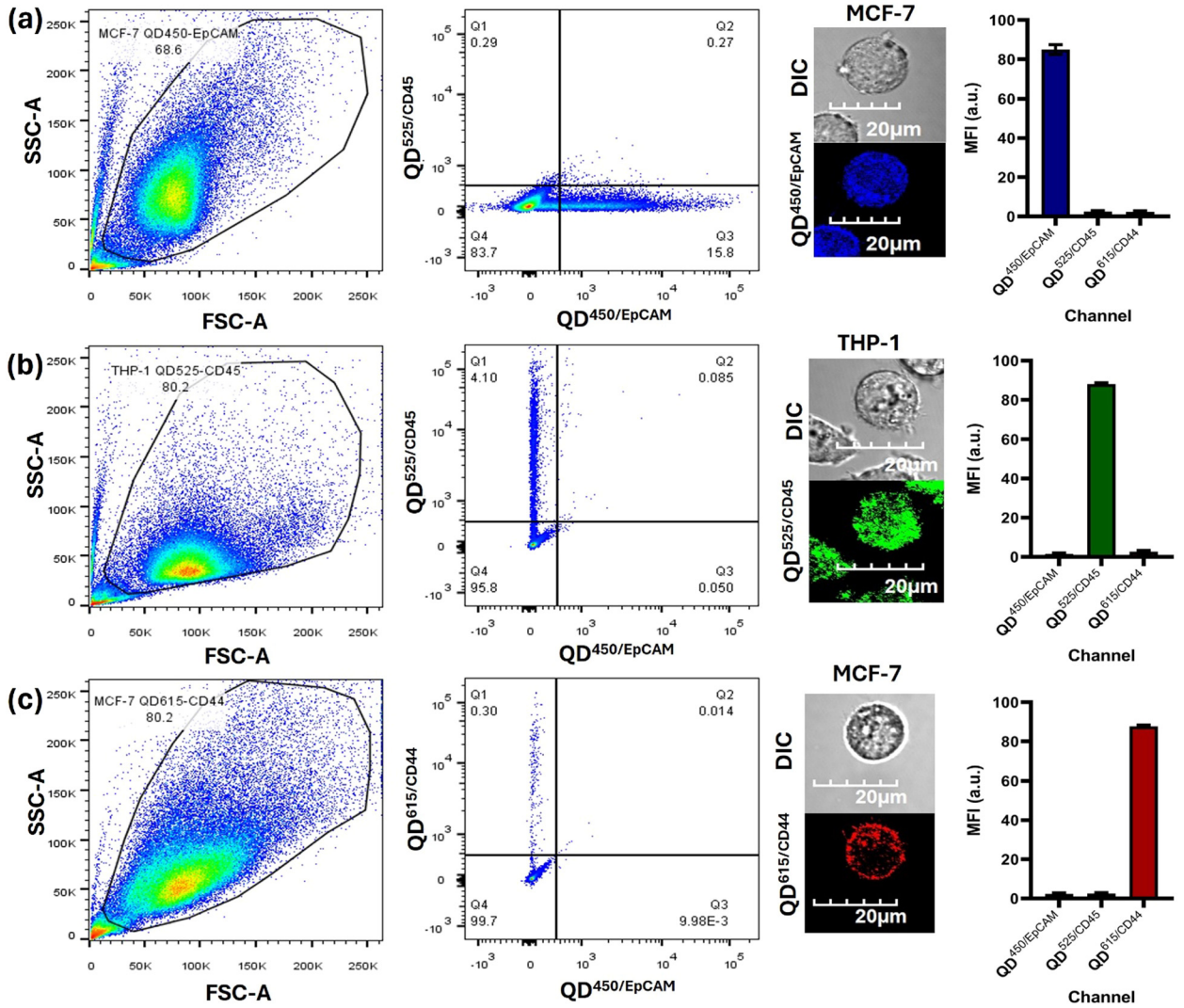

Fig. 3 Optimization of quantum dots for binding to the cell lines specific for the antibody: flow cytometry data of QD^{λ} treated MCF-7 and THP-1 cell line co-cultures. (a) MCF-7 treated with $QD^{450/EpCAM}$, (b) THP-1 cells treated with $QD^{525/CD45}$, (c) MCF-7 treated with $QD^{615/CD44}$. Insets show the respective dot plots and histogram representations for cell sorting (the gating was carried out for fluorescence intensity calculations of the $QD^{\lambda/Ab}$ binding on the specific cell surface).

and CD45+/CD44+ in smaller percentages (0.0995%, 0.025%, and 0.027%, respectively), which are depicted in Fig. 4a. Further investigation using confocal microscopy to measure MFI confirmed these percentages and provided insights into the fluorescence intensity correlating with the specific $QD^{\lambda/Ab}$ on the cells, as shown in Fig. 4b. This calibration process underlined the potential heterogeneity within the co-culture, which was notably consistent after overnight incubation. Subsequent quantitative analysis highlighted in Fig. 4c indicated a statistically significant difference ($p < 0.05$) in the fluorescence intensities between cells treated with $QD^{\lambda/Ab}$ and untreated cells, evidencing the specificity and effectiveness of the $QD^{\lambda/Ab}$ binding. Following the optimization and calibration of the experimental setup, we conducted a series of confirmation tests using triplicates of the co-culture model to ensure consistency and reliability in identifying heterogeneity among the cell populations using $QD^{\lambda/Ab}$ conjugates. Initial results from flow cytometry analysis, as shown in Fig. 5a, demonstrated the distribution of the cells as follows: EpCAM+ cells at 18.7 ± 1.6%, CD45+ cells at 1.60 ± 2.5%, and CD44+ cells at 1.20 ± 2.8%. Additionally, populations co-expressing markers EpCAM+/CD45+ at 1.04 ± 0.5%, EpCAM+/CD44+ at 0.40 ± 0.2%, CD44+/CD45+ at 0.69 ± 0.3%, and triple positive EpCAM+/CD44+/

Table 1 Distribution of the co-culture cell types for $QD^{\lambda/Ab}$ specificity

Cell lines	Specificity[a]	Cells seeded[b]	Mean[c] (%)
MCF-7	$QD^{450/EpCAM}$	1×10^6	15.08 ± 2.01
	$QD^{525/CD44}$		00.30 ± 0.70
THP-1	$QD^{615/CD45}$	1×10^6	04.10 ± 0.82

[a] The concentration of quantum dots is added as per optimal concentration of 40 μg mL^{-1}. [b] Cells are approximately counted to meet the required number for the experiment. For consistency, we used the same number of MCF-7 and THP-1 cell lines in co-cultures. [c] Mean cell counts as per the triplicate of each of the trials run through the flow cytometry study.

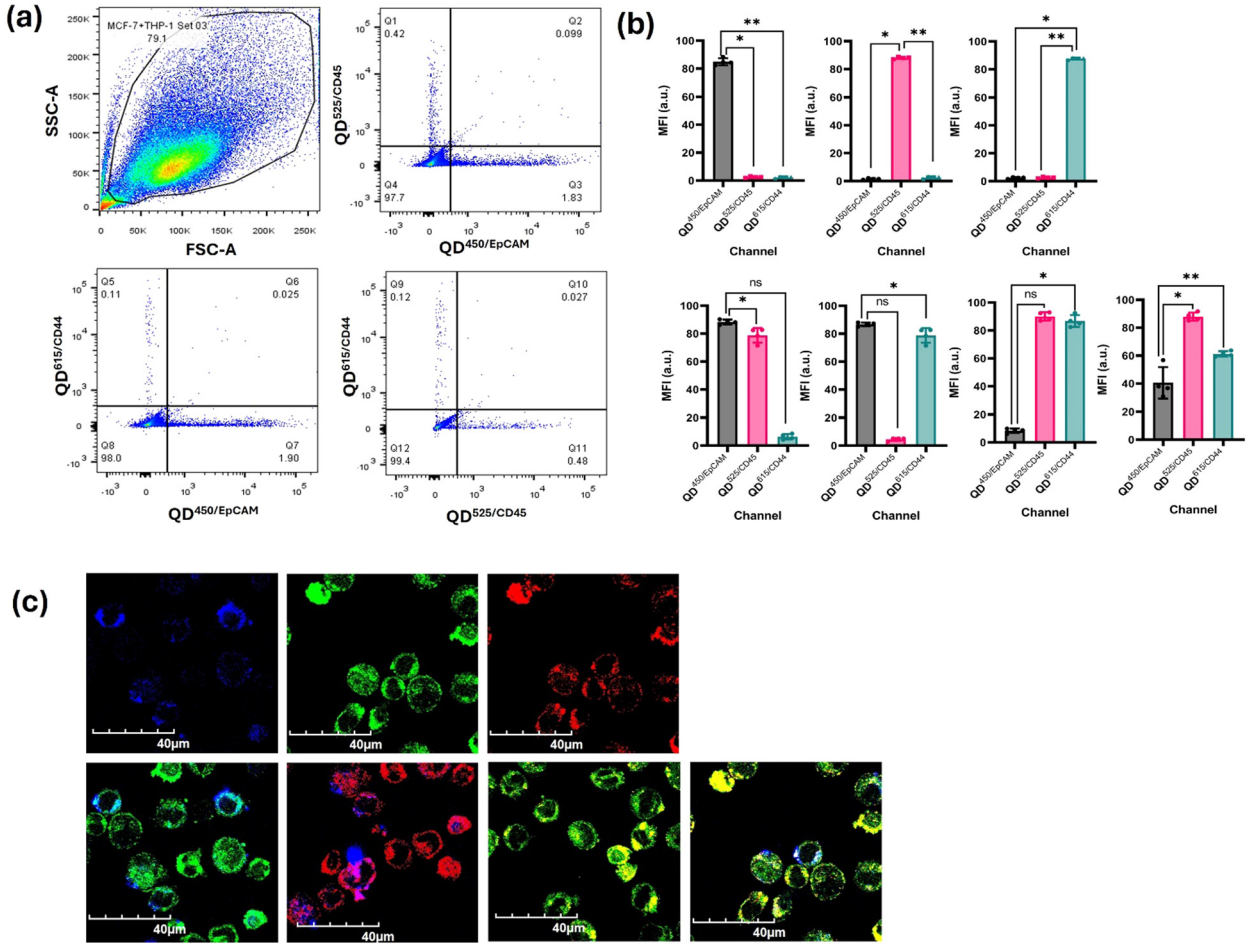

Fig. 4 Calibration of cells binding with $QD^{\lambda/Ab}$ using flow cytometry: (a) cellular sorting data based on the specific antibody conjugate with the cell lines treated to the co-cultures. (b) Confocal laser microscopy MCF-7+ THP-1 cell distribution based on mean fluorescence intensity. (c) Confocal microscopy images of the MCF-7 and THP-1 cell distributions. The statistical data show the probability of the occurrence of the heterogenic cells from the reference through the *T*-test; "*" stands for the significance level of blue and green at <0.05, "**" stands for the significance level of blue and red at <0.05. and "ns" shows the non-significant level at >0.05.

CD45+ at 0.04 ± 0.2% were consistently observed across all triplicate experiments, as shown in Fig. 5b. These findings, detailed in Table 2, confirm the anticipated heterogeneity within the co-cultured cells, underscoring the robustness of our methodological approach in detecting and quantifying specific cellular subpopulations *via* $QD^{\lambda/Ab}$ conjugates, as shown in Fig. 5c.

For this study, we utilized image analysis software, namely Fiji-ImageJ and MATLAB image toolkit, to measure the MFI and generate graphical representations of intensity on a surface, as shown in Fig. 6 (ESI,† Fig. S7). Cells that were labelled with $QD^{450/EpCAM}$ exhibited a wide range of blue fluorescence intensities, which indicates the expression of EpCAM. This contrasted from the limited spectrum of fluorescence found in the MCF-7 cell lines. Significantly, the THP-1 cells exhibited prominent fluorescence peaks on their surface, indicating the elevated levels of CD45 expression, which were characterized by a vibrant green fluorescence linked to $QD^{525/CD45}$. On the other hand, MCF-7 cells that tested positive for CD44+ showed a varied expression of the CD44 antigen. This was characterized by lower levels of red fluorescence intensity from $QD^{615/CD44}$ compared to the blue and green fluorescence, as seen in Fig. 6a–c. Later, the other cell surface observations exhibited different levels of marker expression, displaying distinct and extensive peaks in the combined fluorescence data, indicating a significant amount of possibility in heterogeneity. The observed pattern was similar for all combinations of markers evaluated, including EpCAM+/CD45+, EpCAM+/CD44+, CD44+/CD45+, and EpCAM+/CD45+/CD44+. Detailed observations may be seen in Fig. 6d–g. The ESI† includes further analysis of the fluorescence distribution throughout the three fluorescence channels of the flow cytometer, specifically using the MATLAB Contour and surface plots shown in Fig. S7 (ESI†). These additional data emphasize the diversity and intricacy of the antigen expression among various cell types.[46]

The verified results obtained from our recent studies delved deeply into the heterogeneity of breast cancer cell lines through markers such as EpCAM, CD45, CD44, and their various combinations, and illuminated some of the complex mechanisms underlying cancer metastasis and progression. The expression of EpCAM, typically a marker for epithelial cells and widely used

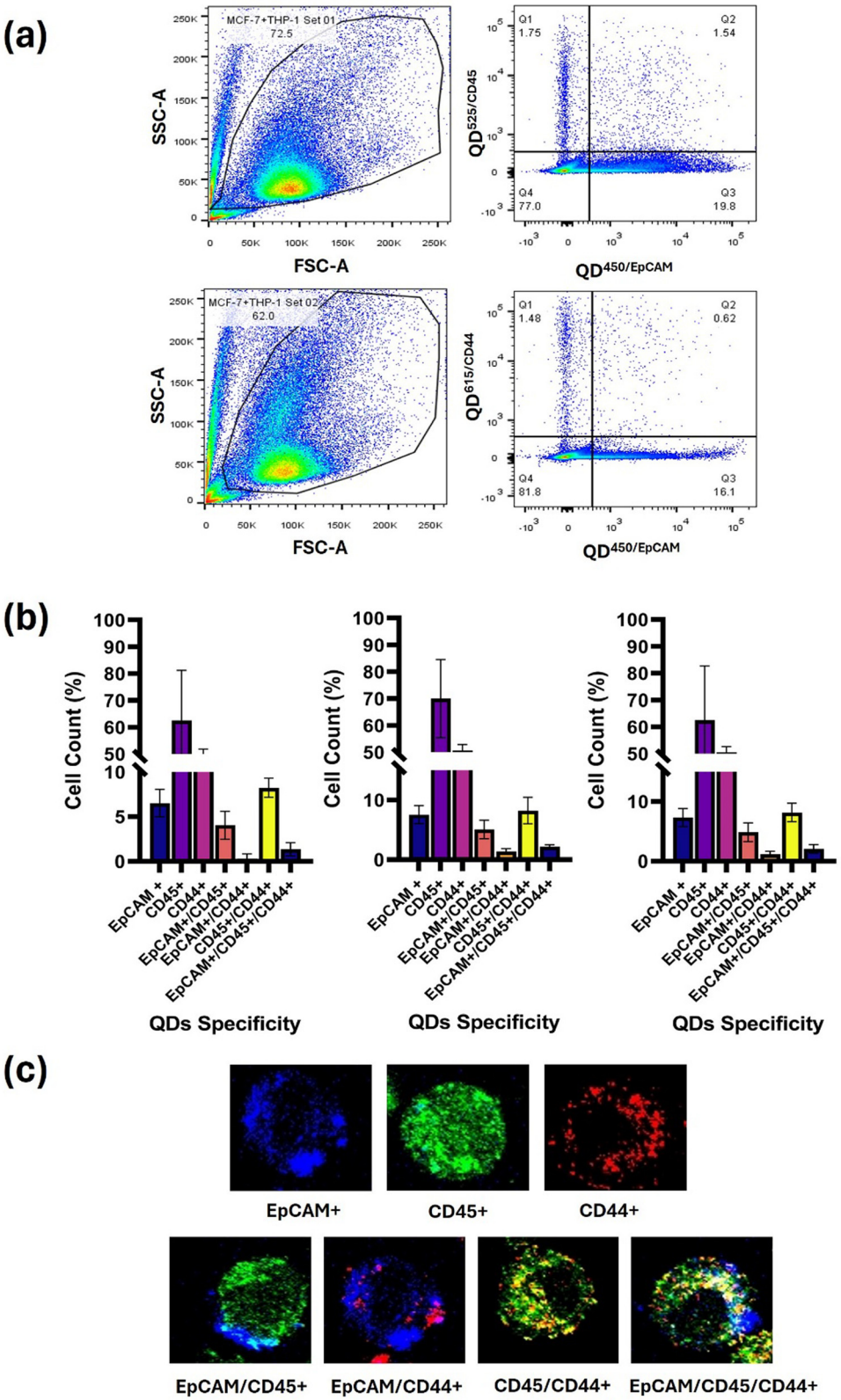

Fig. 5 Identification of heterogeneity in co-culture models: (a) cellular sorting of co-cultures treated with $QD^{\lambda/Ab}$ conjugates (gating was carried out for fluorescence intensity calculations of $QD^{\lambda/Ab}$ binding on the specific cell surface). (b) Mean fluorescence intensity-based determination of the heterogeneity in MCF-7 and THP-1 cells of the cellular sorting and confocal laser microscopy data based on the specific $QD^{\lambda/Ab}$ conjugate with the cell lines treated to the co-cultures. (c) Each of the cell types shown with the specific cell expression with the markers for heterogeneity. The statistical data show the probability of the occurrence of the heterogenic cells; reference through the *T*-test was performed; ''*'' stands for the significance level of blue and green at <0.05, ''**'' stands for the significance level of blue and red at <0.05. and ''ns'' shows non-significance at >0.05.

Table 2 Flow cytometry-based cell sorting

$QD^{\lambda/Ab}$ [b]	Cells sorted[a] (%)	
	MCF-7	THP-1
EpCAM+	19.21 ± 0.60	0.00
CD45+	00.86 ± 0.20	87.7 ± 2.00
CD44+	53.11 ± 1.20	0.60 ± 0.80
EpCAM/CD44+	06.71 ± 0.90	0.09 ± 0.01
EpCAM/CD45+	01.92 ± 0.70	0.20 ± 0.02
CD45/CD44+	01.50 ± 1.00	11.25 ± 0.90

[a] The percentage of cells are estimated with MCF-7 cells seeded at about 1×10^6 cells per mL and the THP-1 cells are about 1×10^6 cells per mL, which mimic the peripheral blood cells. [b] The concentration of the QD^{λ} is added as per optimal concentration of 40 μg mL^{-1}.

for isolating circulating tumor cells (CTCs), varies significantly among breast cancer cells.[47,48] This variability can critically influence the detection and analysis of CTCs. Kwizera *et al.* (2022) demonstrated that a significant portion of mammary CTCs might exhibit low or absent EpCAM expression, potentially leading to an underestimation of CTC populations if EpCAM-based isolation methods are used exclusively.[49–51] CD44 association with cancer stem cells (CSC) and its role in promoting cell adhesion and migration are crucial in the metastatic spread of breast cancer cells.[52–54] CD44 expression correlates with poor prognosis. This is especially evident in the context of gastric cancer, but also significantly relevant in breast cancer.[55] Moreover, the role of CD45s in differentiating leukocytes from tumor cells in samples underscores its importance in assessing immune system interactions within tumors, which is a critical factor in the tumor microenvironment of breast cancer.[56–58]

The exploration of co-expressions (such as EpCAM+/CD44+, EpCAM+/CD45+, and CD44+/CD45+) in breast cancer cell lines reveals the complex cellular phenotypes indicative of various stages or facets of tumor progression. For instance, cells co-expressing EpCAM+/CD44+ might be involved in the epithelial–mesenchymal transition (EMT), enhancing their metastatic capabilities. Brown *et al.* (2020) discussed how the interaction between EpCAM and CD44 can influence cell adhesion and motility, critical factors in cancer progression.[59] Omar *et al.* (2023) discussed how the EpCAM+/CD44+ cancer stem cells in tissue samples from colorectal cancer patients is significantly associated with more aggressive and higher-grade tumors.[60] Similar observations were made in invasive breast cancer cells with a phenotypic variant of cells with EpCAM+/CD44+.[61–63] Akhter *et al.* (2018) identified a drug-resistant tumor cell type with EpCAM+/CD45+ in the ascitic fluid of epithelial ovarian carcinoma patients, originating from the primary tumor and forming the main tumor burden.[64] Sun *et al.* (2022) demonstrated circulating CD45+ EpCAM+ cells as a diagnostic marker for early-stage primary lung cancer.[65] Along with previous subpopulations, Zhu *et al.* (2020) showed the presence of CD45+/CD44+ T cells subpopulations in the non-irritated tumours.[66] Notably, the presence of cells expressing all three markers, *i.e.*, EpCAM+/CD44+/CD45+, might identify a particularly aggressive subset of breast cancer cells with enhanced metastatic potential and the ability to modulate or evade the host's immune response. This is significant as it offers insights into the complex dynamics of tumor biology, and could potentially guide the development of targeted therapies and prognostic tools specifically tailored for breast cancer.

The ongoing advancements in technologies for isolating and characterizing CTCs based on a broad range of markers are critical. Such developments are essential for tailoring personalized treatment strategies for breast cancer, potentially improving clinical outcomes. As our understanding of the interactions between these cellular markers deepens, our approaches to treating breast cancer will continue to evolve, leading to more effective interventions and improved prognostic and therapeutic outcomes in this CCH.

Experimental

Chemicals and regents

All cell culture reagents, including Dulbecco's modified Eagle medium-1X (DMEM), Roswell Park Memorial Institute Medium 1X (RPMI-1640), and foetal bovine serum (FBS), L-glutamine 99% (Glu), and streptomycin/penicillin (Strep/Pen) solution, were purchased from Gibco biosciences. 3-Mercaptopropoinc acid 98% (MPA), ethyl(dimethylaminopropyl) carbodiimide 99% (EDC), *N*-hydroxy succinimide 97% (NHS), NH_2–$(PEG)_8$–COOH (PEG), and streptavidin (SA) were bought from Sigma-Aldrich and SRL Chemicals, ltd. Antibodies, including anti-EpCAM, anti-CD45, and anti-CD44, were purchased from Thermofisher and Abcam, USA.

Preparation of quantum dots

The detailed preparation of the quantum dot antibody conjugates ($QD^{\lambda/Ab}$) is explained in the ESI† (Section S.1). All of the $QD^{\lambda/Ab}$ are prepared in the sequential process, including the synthesis of quantum dots (QD^{λ}) with fluorescence emissions at 450 nm (blue-QD^{450}), 525 nm (green-QD^{525}), and 615 nm (red-QD^{615}), as shown in the earlier research of Vyshnava *et al.*[27,30,31,67] Later, the surfaces of the QD^{λ} were modified with MPA using the biphasic ligand exchange to form active $-COO^-$ ($QD^{\lambda/MPA}$). The EDC/NHS chemical coupling chemical reaction was acquired for (PEG) on the surface of the $QD^{\lambda/MPA}$ ($QD^{\lambda/MPA/PEG}$) to form stable and low cytotoxicity. These PEG coupled $QD^{\lambda/MPA/PEG}$ with SA molecules with the same EDC/NHS coupling chemistry ($QD^{\lambda/MPA/PEG/SA}$). The $QD^{\lambda/MPA/PEG/SA}$ had strong affinity towards the biotinylated antibodies, which involved the following linkages: QD^{450} with anti-EpCAM ($QD^{450/EpCAM}$), QD^{525} with anti-CD45 ($QD^{525/CD45}$), and QD^{615} with anti-CD44 ($QD^{615/CD44}$).

Cell culture preparations

THP-1 (Human monocytic cell line) and MCF-7 (Human breast cancer cell line) were obtained from the National Centre for Cell Science (India). MCF-7 cell lines were cultured in DMEM, whereas THP-1 cells were grown in RPMI-1640, supplemented with 10% FBS, 1 mg mL^{-1} Glu, and 100 μg mL^{-1} Pen/Strep solution at 37 °C in a humidified incubator with a continuous supply of 5% CO_2.

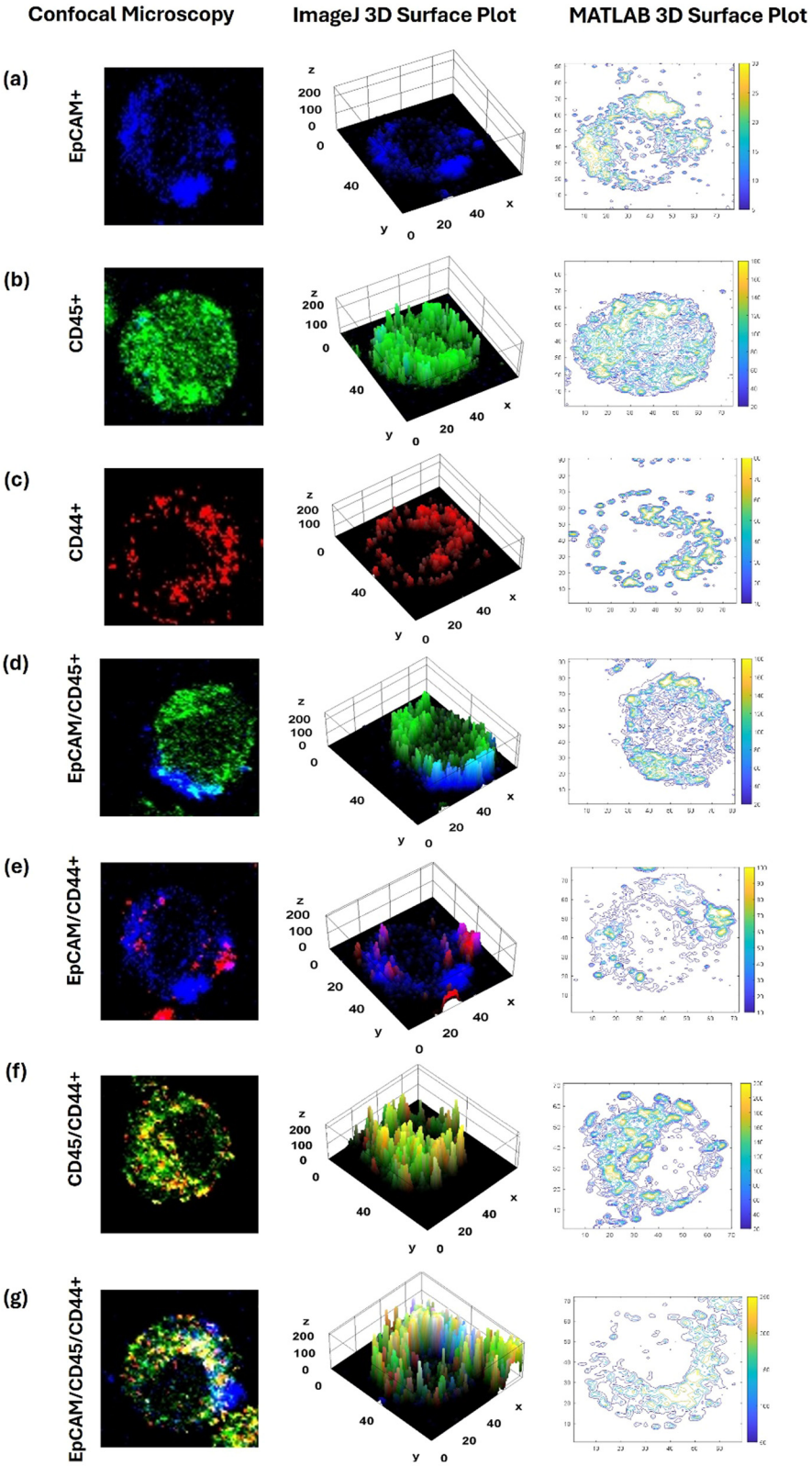

Fig. 6 Heterogeneity in co-culture models based on Fiji-ImageJ and MATLAB 3D surface plots: mean fluorescence intensity determination of the heterogeneity in MCF-7 and THP-1 cells from confocal laser microscopic data based on the specific antibody conjugate to the co-cultures models: (a) EpCAM+, (b) CD45+, (c) CD44+, (d) EpCAM/CD45+, (e) EpCAM/CD44+, (f) CD45/CD44+, and (g) EpCAM/CD45/CD44+.

Co-culture preparations

This study employed a co-culture system using Transwell® inserts in 12-well plates to investigate the interactions between the tumours and the immune system. MCF-7 epithelial cells were cultivated in the bottom chambers, while THP-1 immune cells were positioned in the Transwell® inserts above the epithelial cells. This configuration facilitated intercellular communication *via* soluble chemicals while maintaining physical separation between cell types, which is essential for studying paracrine effects and replicating tissue spatial organization. The co-cultures were kept in a humid incubator at a temperature of 37 °C with an environment containing 5% CO_2 for durations ranging from 24 to 48 h, depending on the specific needs of the experiment. During this incubation period, the level of cell confluence was regularly observed to get a coverage of 60–80% before doing additional analyses. This method was developed to augment our comprehension of the intricate interplay between the tumor cells and immune cells, offering valuable insights into the advancement of cancer and the reactions to therapies.

Flow cytometry assay

Each co-culture combination was seeded on a 6-well culture plate at 1×10^6 cells per well for the flow cytometry test in triplicate studies. For 24 h, the cells were permitted to incubate under optimal cell culture conditions, as mentioned above. The culture medium was replenished, and the prepared $QD^{\lambda/Ab}$ was incubated in the wells according to the optimized protocol.[27,31] The cells were washed with 1X PBS and allowed to settle for 5 min before being treated with EDTA solution, which is less harmful to cells than trypsin, and then suspended in 1X PBS at 4 °C. Using a multi-laser scan flow cytometry and sorting experiment, the fluorescence intensity of each $QD^{\lambda/Ab}$ binding was then assessed with a flow cytometer (FACS Jazz, Becton Dickinson Co.).

Confocal microscopy

The prepared co-cultures with healthy confluency (≥60–80%) cells are rinsed in 1X PBS. Later, 1 mL of specific $QD^{\lambda/Ab}$ was added at optimal concentrations, which were dispersed in the fresh DMEM (without phenol red and FBS), as shown in the ESI† Table S3. The cells were allowed to incubate for 20–30 minutes, followed by carefully rinsing the cells with 1X PBS to remove excess $QD^{\lambda/Ab}$. Later, 1 mL fresh 1X PBS was added to the co-cultures, followed by observing the cells under a confocal laser scan microscope (FV1000, Olympus Co.).[27] Through the use of conventional and autonomous modes on a confocal laser microscope with 405 nm laser excitations, the fluorescence emissions of the respective $QD^{\lambda/Ab}$ were observed at magnifications from 10X, 40X, and 60X. Olympus flow view FVW-ASW software was used to collect and process the RAW image files. For future usage, cells were stored in 90% paraformaldehyde at 4 °C.

ImageJ and MATLAB measurements

The required confocal images were retrieved using ImageJ (Fiji ImageJ version v1.53o). The histogram manipulation was used to pre-process the confocal images, among other properties. Image attributes were extracted when the ROI (region of interest) selection was made. In a 3D surface plot plugin, the picture properties including the fluorescence are utilized to determine its intensity peak maxima. The software interface allows for smoothing, noise reduction, scaling, and perspective modifications to the surface plot. The same image process was made using the RGB extraction from the respective images by using the RGB image extraction program (a detailed description of the program had given in the ESI†).[68–70] The extracted image details are used to generate plots using the contour, contour RGB, images, and 3-D surface, which are prebuilt in the MATLAB program console (MATLAB R2019b).

Statistical modelling

GraphPad Prism 5 (GraphPad Software, USA) and Origin 8.0 (Origin Lab, USA) were used for statistical and data analysis. All data were then presented using the mean standard deviation of three separate trials. To determine the statistical significance, simple linear regression, a one-way analysis of variance was utilized, followed by a *t*-test (Tukey's range test). Differences were considered significant when the p value was < 0.05.

Conclusions

The results of our research show that $QD^{\lambda/Ab}$ conjugates are effective in detecting and studying cellular heterogeneity in co-culture models of MCF-7/THP-1 cells. The precise attachment of quantum dots linked with antibodies to specific cancer cell markers allowed for a thorough analysis of cell populations, and revealed significant heterogeneity based on the expression of these cellular markers. These conjugates have demonstrated their effectiveness as an accurate method for detecting biomarkers, which could potentially assist in the specific therapy and diagnosis of cancer. Combining modern imaging techniques with surface chemistry provides a promising method to improve the precision and practicality of biomolecular probes in clinical oncology.

Author contributions

Conceptualization, data curation, formal analysis, methodology, visualization, and writing of this manuscript were performed by Mr Satyanarayana Swamy Vyshnava; project administration, resources, software, supervision, validation and proofreads were done by Prof. Surendra Babu Numbury, Dr Obula Reddy Chittepu, Dr Kamala Prasad Vasikarla, Prof. Roja Rani Anupalli Vasu, Dr Govardhana Reddy Peddiahgari, and Prof. Muralidhara Rao Dowlathabad.

Conflicts of interest

There are no conflicts to declare.

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REVIEW

Harnessing probiotic foods: managing cancer through gut health

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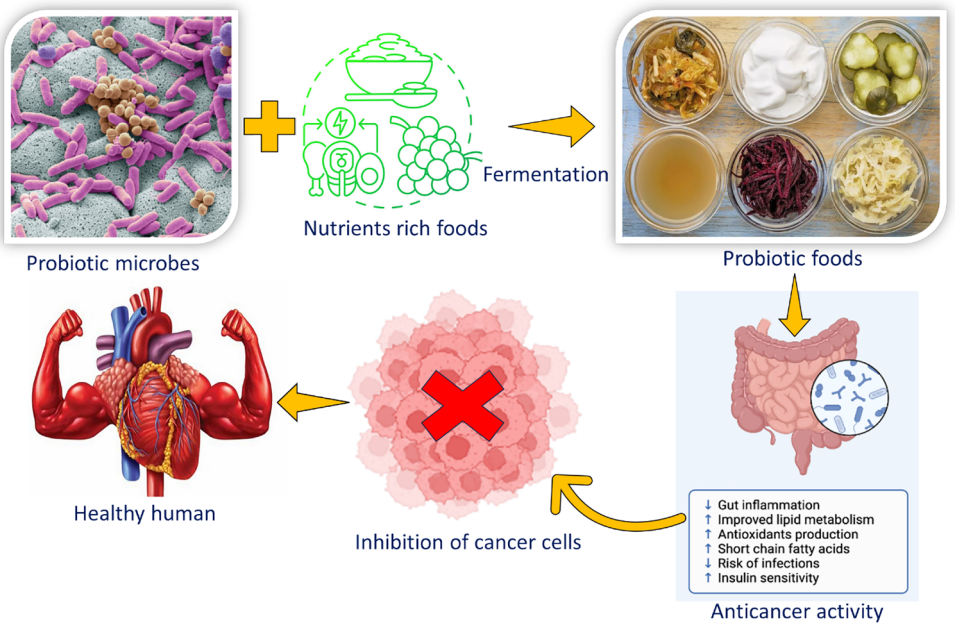
Abstract

One of the greatest threats to global health is cancer. Probiotic foods have been shown to have therapeutic promise in the management of cancer, even though traditional treatments such as radiation therapy, chemotherapy, and surgery are still essential. The generation of anticarcinogenic compounds, immune system stimulation, and gut microbiota regulation are a few ways that probiotics when taken in sufficient quantities, might help health. The purpose of this review is to examine the therapeutic potential of probiotic foods in the management of cancer. Research suggests that certain strains of probiotics have anticancer effects by preventing the growth of cancer cells, triggering apoptosis, and reducing angiogenesis in new tumors. Probiotics have shown promise in mitigating treatment-related adverse effects, such as diarrhea, mucositis, and immunosuppression caused by chemotherapy, improving the general quality of life for cancer patients. However, there are several factors, such as patient-specific features, cancer subtype, and probiotic strain type and dosage, which affect how effective probiotic therapies are in managing cancer. More research is necessary to find the long-term safety and efficacy characteristics of probiotics as well as to clarify the best ways to incorporate them into current cancer treatment methods.

Graphical abstract

Graphical representation showing the role of probiotic foods in cancer management.



Keywords Microbiome · Probiotics · Anticancer · Fermented foods · Metabolites

Extended author information available on the last page of the article

Introduction

Cancer is caused by cells that have escaped the normal division route and continue to divide and grow abnormally. The uncontrolled growth of these cancer cells may be restricted, or they may also spread to other organs (malignant) (Hanahan, 2022). The cluster of these cancer cells is called a tumor. There are several types of cancer, including lung, breast, mouth, brain, and colorectal cancers. Breast cancer in women and prostate cancer in men are the two most common types of cancer. Lung and colon cancers are common in both sexes (Mattiuzzi and Lippi, 2019). The diagnosis provides information about the stage of cancers, how much it has spread, and which vital organs it has affected. Cancer treatments have advanced over the past few decades, but an entirely effective treatment has yet to be identified. This is difficult to achieve, as cancer is a combination of several diseases. This leads to several conditions, each with some common symptoms and some entirely different symptoms. The therapies for cancer treatment include surgery (removal of tumors by surgery), chemotherapy (the use of chemicals to kill cancer cells), and radiation (the use of X-rays to kill cancer cells). These treatments can significantly reduce cancer incidence, but there are several side effects of these treatments. To increase the success of the treatment and mitigate the side effects, doctors and researchers are focusing on an integrated treatment where other therapies such as acupuncture, naturopathy, and nutrition are also being blended. The target is not only to cure cancer but also to treat the pain, fatigue, and mental strain that accompany cancer in each patient (Hanahan and Weinberg, 2021; Hanahan, 2022).

The microbiome refers to the population of microbes that live in the human body, especially in the gut. A strong microbiome consisting of healthy microbes affects the health of the individual and helps in fighting several diseases (Altveş et al., 2020). They affect immunity, protect against disease-causing bacteria and are also responsible for the production of vitamins such as B-complex and vitamin K (needed for blood coagulation. Probiotics consist of live microorganisms that may provide health benefits when consumed. They are typically present in yogurt, various fermented foods, and dietary supplements. These microbes enhance the gut microbiome and help the body fight against diseases. Recent studies have shown that the gut microbiome can influence the host's response to chemotherapeutic agents by enhancing the efficacy of chemodrugs and mediating chemotherapy-induced side effects and toxicity through several mechanisms (Kalasabail et al., 2021). The microbiome can suppress tumors and strengthen the immune system through mechanisms such as anti-inflammation, barrier functions, synthesis of antioxidants, vitamins, fatty acids, and production of other beneficial metabolites. Dysbiosis of the microbiome leads to inflammation, gut permeability, barrier failure, DNA damage, exposure of bacteria to the circulation, and the development of bile acids, endotoxins, and excess conjugated estrogen. All these actions promote the development of tumors leading to cancer (AlHilli and Bae-Jump, 2020). Research performed on the gut microbiome and genetically predisposed mice against leukemia has shown that an intact microbiome protects mice against this disease. Murine models of precursor B-cell acute lymphoblastic leukemia (pB-ALL) were used to show that microbiome deprivation by antibiotic treatments triggered leukemia in the absence of an infectious stimulus. The use of full-length RNA sequencing of fecal samples showed that genetic susceptibility to pB-ALL was affected by a distinct gut microbiome. Machine learning and GC−MS studies revealed that a lack of commensal microbiota promotes leukemia in genetically predisposed mice rather than the presence of any specific bacteria (Vicente-Dueñas et al., 2020). Various gut bacteria are involved in the regulation of the efficacy and toxicity of chemotherapy drugs. For example, oral supplementation of *Lactobacillus* lowers the toxicity of cisplatin, and *Enterobacter* and *Pseudomonas* metabolize the drug gemcitabine to 2',2'- difluorodeoxyuridine (Wu et al., 2019; Geller et al., 2017).

Yogurt, kefir, sauerkraut, tempeh, kimchi, miso, kombucha, pickles, buttermilk, and natto are some of the most popular probiotic foods consumed worldwide. Probiotics survive in the intestine after being consumed and have proven health benefits. The microbes present in probiotics also assist in the breakdown and absorption of medications taken by patients. The consumption of probiotic foods has been linked to lowering the risk of cancer and mitigating its effects.

Probiotic foods-a potential alternative therapy for cancer

Probiotics are known to impart several health benefits to the human body. Probiotics can regulate the gut microbiome, degrading potential cancer-causing substances and strengthening the immune system. Probiotics outgrow the pathogenic microbes that grow in the gut, resulting in the exclusion of pathogens. The probiotics colonize the gut epithelium and do not allow the pathogenic bacteria to fix on those sites. Studies on different microbes that have been shown to have positive effects on different types of cancers have been performed (Nazir et al., 2018). Probiotics can be lactic acid-producing bacteria, nonlactic acid-producing bacteria or yeasts. *Lactobacillus, Enterococcus, and Lactococcus* are some of the most common bacterial

probiotics. Probiotic yeasts include *Bacillus* spp., *Saccharomyces cerevisiae, Pichia,* etc. (Bedada et al., 2020). The anticancer and antimutagenic activity of probiotics is due to several mechanisms, such as binding with mutagens and degrading and inhibiting mutagens, preventing nontoxic procarcinogens from converting into harmful and toxic carcinogens, and strengthening the immune system of the individual by secreting certain anti-inflammatory substances (Raman et al., 2013). They also produce certain antimicrobial substances that have proven therapeutic effects on cancer patients. Bacteriocins are antimicrobial peptides produced by gram-positive bacteria. These compounds are nontoxic and cause no side effects on the human body. Nisin is one of the most common bacteriocins. It can perforate cancer cell membranes, promote apoptosis, and obstruct cancer cell generation (Molujin et al., 2022). Bacteriocins are able to act against cancer cells because they can differentiate between cancer and noncancer cells. The cell membrane surface of cancer cells is negatively charged, whereas that of noncancer cells is neutrally charged (Molujin et al., 2022). Probiotics also produce deconjugated bile acids, which are byproducts of bile salts. These acids have powerful antimicrobial properties in comparison to the normal bile salts produced in the human body (Oelschlaeger, 2010). The overall number of clinical studies on cancer and probiotics published in PubMed in the past 20 years has been shown in Fig. 1.

Probiotic bacteria can also detoxify and biotransform carcinogens and procarcinogens into less toxic substances, thus preventing the formation of tumors. This process of biotransformation occurs in the gut via enzymes. These enzymes are modulated by dietary agents, which depend on the type of diet a person consumes (Raman et al., 2013). Strains of certain bacteria, such as *Lactobacillus acidophilus* and *Bifidobacterium,* can decrease the activity of enzymes (β-glucuronidase, nitro reductase, and azo reductase) that regulate the process of carcinogenesis (Raman et al., 2013).

The metabolites produced by prebiotics maintain homeostasis in the gut and increase the growth of beneficial bacteria that restrict the formation of carcinogens from procarcinogens. They decrease the levels of harmful enzymes such as β-glucosidase, β-glucuronidase, and nitroreductase. Postbiotics include metabolic byproducts synthesized by live microorganisms, including bacteriocins, hydrogen peroxide, exopolysaccharides, and bacteriocins, or products released after bacterial lysis, including exopolysaccharides, cell surface proteins, muropeptides, and teichoic acids. Many these postbiotics have shown the ability to enhance antitumor activity, immunity, and antisepsis. In the past few years, postbiotic metabolites have gained popularity in medical

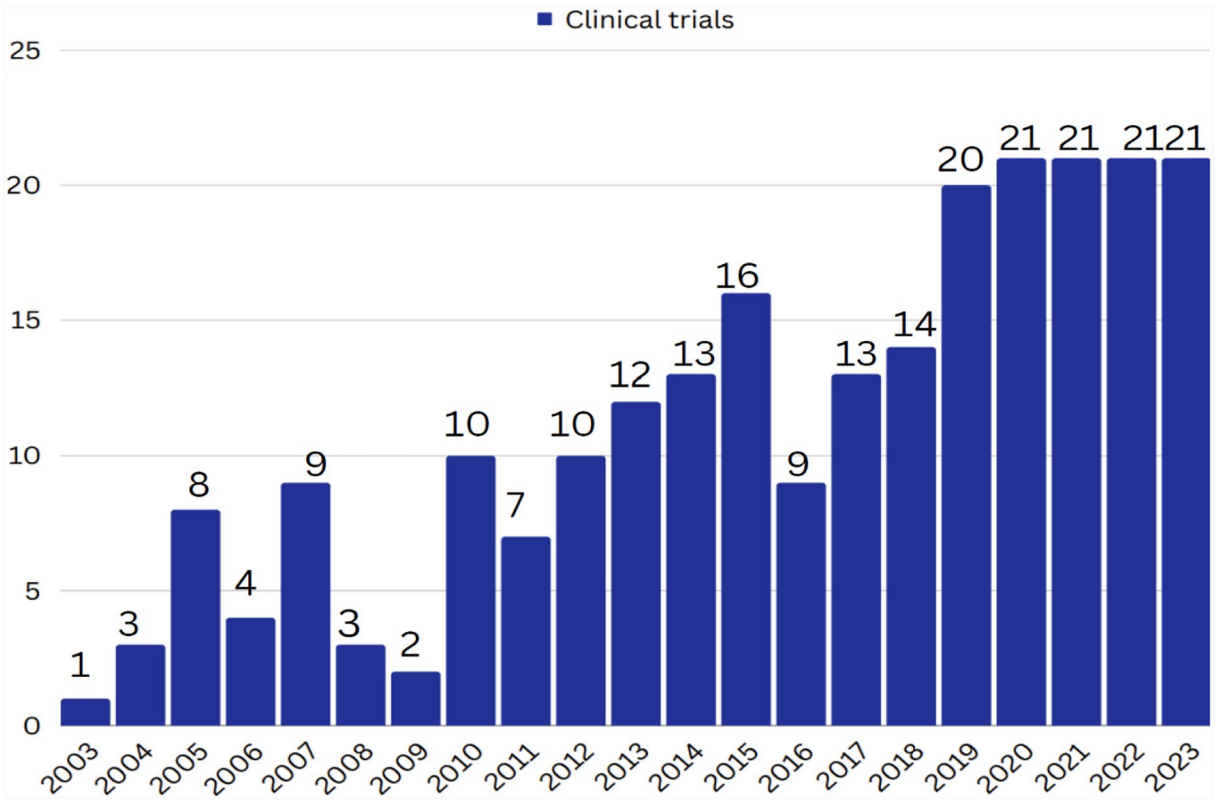


Fig. 1 Graph showing the overall number of clinical studies on cancer and probiotics published in PubMed in the past 20 years

treatments due to their understandable chemical structures, long shelf life, anti-inflammatory properties, and antiproliferative effects. The most common example is *Lactobacillus* species, which produce compounds that inhibit the growth of MCF7 breast cancer cell lines and inhibit the proliferation of pancreatic tumor cell lines through the action of polysaccharides (Noroozi et al., 2021). Synbiotics are combinations of both pre- and probiotics in a single form. These compounds can regulate various metabolic pathways, promote apoptosis, inhibit proliferation, and promote the formation of short-chain fatty acids. A recent study in mice showed that supplementation with a specific symbiotic dose suppressed colorectal cancer in test models. Intervention with synbiotics formed an intestinal barrier and inhibited cancer occurrence by upregulating the expression of anti-inflammatory cytokines and tight junction proteins and downregulating the expression of inflammation-causing cytokines. Synbiotics also improved the colonic microbiome of mice, promoting the development of short-chain fatty acids and secondary bile acids (Wu et al., 2023).

A better understanding of cancer biology and the action of probiotics in the control of cancer can help researchers find a solution for the management of this deadly disease more strategically.

Probiotics and fermented foods

Probiotics are live microorganisms that, when consumed, provide benefits to humans by supporting the intestinal microbial balance. Fermented foods have different microorganisms grown during the fermentation process. The action of these microbes results in the formation of various compounds including organic acids and alcohol which have the ability to inhibit spoilage in fermented foods and also improve the health of people who intake such foods regularly. The bacteria found in these fermented foods play a key role in human health, especially in the digestive tract, and are known as probiotics. They can enhance immunity against pathogenic bacteria. Lactic acid bacteria (LAB) produced in fermented foods are suitable probiotics that can replace antibiotics by overcoming pathogenic bacteria. Several fermented foods are good sources of these probiotics, including Brem and Rusip from Indonesia, Kimchi and Gochujang from Korea, Kefir from Russia, and Ergo from Ethiopia among others (Soemarie et al., 2021). Fermented foods are often labeled and matketed as "probiotic foods" and "contain probiotics". These labels show that the foods have live, health-promoting microbes. However, the term "probiotic" should be used only if the health benefit has been proved by a well-defined live microorganism. The final food product should also have enough microbial strains known to impart specific health benefits. For example, sauerkraut has multiple strains of *Lactiplantibacillus plantarum* (previously *Lactobacillus plantarum*) which are unidentified and uncharacterized. But, if an *L. plantarum* 299v strain which has been genetically characterized and clinical demonstration has been shown, will remain present in the efficient dose until the product is consumed, the sauerkraut will meet the minimum requirement to be labeled as a probiotic fermented food. It can then be labeled and sold as "Probiotic sauerkraut with *L. plantarum* 299v can improve intestinal well-being". In some cases, if the stain is not specific, a label "contains probiotics" can be used. This will be allowed only if at least one strain from the fermented food meets the criteria mentioned above. For some common species like *Bifidobacterium* and *Lactobacillus*, the "probiotic foods" term can be used, provided they provide a minimum of 10^9 colony-forming units (CFU) in each serving (Marco et al., 2021). Yogurt containing *Lactobacillus delbrueckii* subsp. *bulgaricus* and *Streptococcus thermophilus* should have 10^7 CFU/g until its expiry date. The European Food Safety Authority has allowed the health claim on yogurt that it contains live bacteria which improve lactose digestion in people suffering from lactose maldigestion, with the condition that the yogurt contains a minimum of 10^8 CFU/g of the live starter culture by the end of the shelf life. For any fermented food to be used and labeled as a 'biotic' (pre or pro), the product should be characterized, tests should be done on the health benefits. The genome sequencing must have been done to identify and name the microorganism responsible for the probiotic action (Vinderola et al., 2023).

Understanding cancer and its management

Research on cancer management has been ongoing for several decades. There is no accurate cure for this disease. The treatments available are only a way to reduce the effect of cancer and not eliminate it. Additionally, these treatments leave patients with other side effects that add to the already deteriorating health conditions of cancer patients. Understanding cancer at the cellular level might help in finding the relationship between probiotics and their potential to manage cancer at an early stage.

Understanding cancer biology

Worldwide, more than 18 million people are diagnosed with cancer. Among the four major types, breast cancer, lung cancer, colorectal cancer, and prostate cancer are the most common (Hesketh, 2023). A cancer cell is a normal body cell that has undergone a series of changes and escaped the normal route followed by other noncancerous cells. Cancer cells develop into tumors, and tumors transform into cancerous masses over time. Several genetic and lifestyle factors promote the formation of cancer cells. Genetic mechanisms

include chromosomal translocation (Bcr gene and Abl oncogene in blood cancer), point mutation (Ras gene- colon cancer), deletion (Erb-B gene; breast cancer), amplification (N-myc in neuroblastoma), and insertion activation (in acute blood cancer). Similarly, chronic blood cancer in elderly people occurs through the exchange of genetic materials between chromosome numbers 9 and 22. This causes the formation of a ph1 biomarker, which is detected in approximately 95% of patients (Hassanpour and Dehghani, 2017). Mutation of the p53 gene leads to the development of cancer cells. Abnormal p53 gene expression has been detected in more than 60% of cancer cases. Normally, this gene plays a role in normal cell division, cell differentiation, and death (Hassanpour and Dehghani, 2017).

Cell apoptosis is a major factor in maintaining a fine balance between cell survival and death. Cancer cells escape apoptosis, which causes uncontrolled growth and enlargement of cancerous masses in the body (Goldar et al., 2015). An imbalance between the antiapoptotic and proapoptotic B-cell lymphoma-2 (Bcl-2) protein families lead to the survival of cancer cells (Kang and Reynolds, 2009). In several cancer patients, genetic and epigenetic remodeling of the proapoptotic members of the Bcl protein family has been detected. Inactivation of these proapoptotic proteins and an increase in the levels of antiapoptotic proteins are other reasons for the evasion of cancer cell apoptosis. There is enough scientific evidence indicating that the dysregulation of microRNAs (miRNAs) is related to human cancer. miRNA-21, miRNA-17/92, miRNA-272/273, and miRNA-221/222 negatively control apoptotic activity and enhance the rate of cancer cell growth and resistance to cancer treatment drugs (Goldar et al., 2015). Another mechanism that leads to the development and proliferation of cancer is inflammation. Inflammation promotes cancer and occurs even before the formation of a tumor. The association between cancer and inflammation has been scientifically proven, as leukocytes have been detected in tumors. For example, inflammatory diseases such as inflammatory bowel syndrome, chronic hepatitis, and bladder inflammation all increase the risk of developing colorectal cancer, liver cancer, stomach cancer, and bladder cancer. Several environmental factors also promote inflammation, which leads to the development of cancer. Alcohol consumption, smoking, obesity, and a sedentary lifestyle are factors that promote inflammation in the body (Greten and Grivennikov, 2019).

It has also been reported that cancer cells can ingest noncancerous cells. This theory has been supported by the detection of cells in cell structures in several cancers. Cancer cells ingest neighboring cells, leading to the spread of cancer to other organs and parts of the body (Fais and Overholtzer, 2018). This trait of cancer cells was detected when tumor cells exhibited a crescent-shaped nucleus and another smaller cell within a large vacuole. This process is referred to as cancer cell cannibalism. Like any other unicellular entity, cancer cells need nutrients for survival. Nutrient requirements are increased in cancer cells because the tumor vasculature is deficient, as observed in many cancers. This leads to the engulfment of nearby cells by cancer cells to fulfill their nutrient requirements in bulk. This property is acquired by cancer cells in later stages of cancer progression, as was observed in metastatic cells and not in cells that arose from primary tumors. (Fais and Overholtzer, 2018) Cannibalism activity has also been seen in the breast cancer cell line MDA-MB-231, which cannibalizes mesenchymal stem cells (Bartosh et al., 2016). Cannibalism is similar to phagocytosis, the major difference being that cancer cells engulf both live and dead cells. Cell-in-cell mechanism or cannibalism has been seen in several types of cancers, such as blood cancer, breast cancer, skin cancer, lung cancer, ovarian cancer, prostate cancer, and urinary tract cancer (Fais and Overholtzer, 2018).

Current approaches to cancer treatment

Chemotherapy, radiation therapy, and surgery are common methods for treating cancer. Targeted therapies, immunotherapy, hormonal therapy, cryotherapy, laser therapy, photodynamic therapy, and hyperthermia are other alternatives. Tumors are removed by surgery, cancer cells are eradicated by chemotherapy, and X-rays are used in radiation. Treatments can be mixed according to the needs of the patient and the stage of malignancy. Three stages of chemotherapy are used to treat cancer: primary, neoadjuvant, and adjuvant. When there are no other options for treating advanced-stage cancer, primary chemotherapy is used. Neoadjuvant chemotherapy decreases tumor size before surgery and is used for localized tumors such as breast and rectal cancer. Adjuvant chemotherapy is often administered for stomach, breast, and colon cancers to improve survival and lower recurrence (Chu and Sartorelli, 2018).

Repeated doses of chemotherapy drugs are used to inhibit cell proliferation. Cytotoxic drugs target the S phase of the cell cycle, while others restrict spindle formation during the M phase. Alkylating agents, such as bendamustine and cisplatin, inhibit DNA replication and transcription by generating unstable alkyl groups that react with nucleophilic centers in proteins and nucleic acids (Amjad et al., 2023). Antimetabolites, including cytidine analogs and folate antagonists, inhibit DNA synthesis and repair. Antibiotics like daunomycin and bleomycin also inhibit DNA and RNA synthesis. Additional drugs like hydroxyurea and tretinoin are used for their unique mechanisms. Combination therapy, using multiple drugs, maximizes effectiveness but often causes side effects like fatigue, nausea, and hair loss (Amjad et al., 2023).

The discovery of X-rays by Wilhelm Röntgen in 1895 revolutionized cancer treatment with radiation therapy, which is used in about 50% of cancer cases (Baskar et al., 2012). Radiation therapy, often combined with surgery and chemotherapy, plays a major role in killing cancer cells by damaging their genetic material, preventing further growth. Radiotherapy targets cancer cells while minimizing exposure to normal cells and can be applied before or after surgery to manage tumors. Radiation is delivered as external beam radiation, using high-energy photons, protons, or particle rays, or as internal radiation, placing radioactive substances directly into tumors (Baskar et al., 2012). Early cancers like skin, lung, prostate, and cervical cancers are curable with radiation alone, while others require combined treatments. Advanced techniques such as 3D radiation and intensity-modulated radiation therapy (IMRT) enhance precision, safeguarding vital organs and targeting tumors. Radiation treatments are typically administered over weeks or months (Allen et al., 2017).. Surgical treatment involves removing tumors and surrounding healthy tissue. Laparoscopic surgery, with minimal incisions and camera guidance, provides a detailed tumor view. Surgery type depends on tumor size and patient preference, aiming to relieve pain and discomfort caused by tumors pressing on nearby body parts (Abbas and Rehman, 2018).

Anticancer mechanism-cellular mechanism and immunity enhancing effects/tumor suppressing action

Probiotics influence the gut microbiota and contribute to the well-being of the human body. They support a balance by reducing the number of diseases causing microbes and do not allow them to deplete the nutritional sources and habitat in the gut. Probiotics play a pivotal role in enhancing the immune system by interacting with the T cells and dendritic cells in the lymphoid tissue associated with the gut. They do so by modulating and activating the immunological responses (Yousefi et al., 2019). This activation results in the release of cytokines which suppress the inflammation-inducing factors and enhance the anti-inflammatory response. They regulate the innate immune cells like natural killer (NK) cells, macrophages, and dendritic cells (Gui et al., 2000). This regulation helps in enhancing the antimicrobial action of the cells. The probiotics influence the T and B cells activity. They promote the development of regulatory T cells responsible for immunological actions and boost the B cells to produce more IgA immunoglobulin antibodies. These actions contribute to the immune-enhancing property of probiotics. Probiotics also fortify the barrier property of the gut epithelial tissue by reducing the permeability of pathogenic microbes, contributing to overall health. The probiotics also prevent the development and inhibit the activity of pathogenic viruses and bacteria in the digestive tract (Liu et al., 2020) Certain probiotics can regulate the acidity of the stomach, making an unfriendly environment for the growth of pathogenic microbes. Probiotics suppress the production of inflammation-causing cytokines like interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF) (Zhou et al., 2024). The short-chain fatty acids (SCFA) produced by the probiotics inhibit pathogen growth. The SCFA encourages the epithelial cells to produce antibacterial peptides thus stabilizing the intestinal barrier property. They regulate the tight junction proteins and seal the top epithelium and endothelium thus strengthening the epithelial permeability and preventing damage to the epithelial structure. They also restore the abnormal transepithelial resistance caused by pathogenic lipopolysaccharides leading to a reduction in inflammation and excessive apoptosis. Certain probiotic strains also regulate the T helper cells 17 (Th17) and encourage the secretion of IL-17 alpha which in turn triggers the type 3 lymphocytes to produce IL-22. IL-22 is an important immune defense cytokine that maintains intestinal homeostasis and also promotes tissue regeneration and healing (Cristofori et al., 2021). Probiotics occupy the spaces available on the intestinal wall leaving no space for the pathogens. Conjugated linoleic acid (CLA) induces the expression of apoptosis genes-Bcl-2, capsases3, and 9 thus inhibiting the spread of colon cancer cells. Probiotics significantly reduce the *Fusibacter* genus which is a major factor responsible for tumorigenesis (Lu et al., 2021). By activating pro-caspases and modifying the expression of pro-apoptotic (Bax) and anti-apoptotic (Bcl-2) proteins, probiotics such as *Lactobacillus* and *Bifidobacterium* strains can overcome apoptosis resistance in cancer cells and ultimately induce apoptosis in tumor cells. Probiotics protect cells from oxidative damage and oxidative stress, which are connected to the development of cancer. They do this by expressing antioxidant enzymes, binding reactive oxygen species (ROS), releasing antioxidants, and chelating transition metals (Nowak et al., 2019). Short-chain fatty acids (SCFAs), such as butyric acid, act as a carbon source for healthy colonocytes and increase the activity of glutathione transferase (SGT), which is responsible for the increase in apoptosis in tumor cells. This process helps eliminate tumor cells without inflaming or harming surrounding healthy cells. Other SCFAs like acetate, propionate, and butyrate interact with G protein-coupled receptors 43 of T helper1 cells or inhibit histone deacetylases (HDACs) of cytotoxic T lymphocytes to exert immunotherapy effects. SCFAs mediate the differentiation and function of regulatory T cells, influence cytokine production in the tumor immune microenvironment (TIME), and modify epigenetic regulation of CD8 + T cells by inhibiting HDACs. Butyrate enhances anti-tumor activity by inhibiting class I HDAC activity, slowing proliferation, promoting apoptosis, improving intestinal integrity, and affecting cancer stromatogenesis

(Dong et al., 2023). In terms of oral cancer, probiotics modulate the oral microbiome composition, promoting the growth of beneficial bacteria like *Lactobacilli spp*. and inhibiting the growth of pathogenic species such as *Streptococcus mutans* and *Candida albicans*. They produce biofilms that possess antibacterial properties, inhibiting the growth and colonization of oral pathogens within the oral cavity, and protecting against oxidative damage. They also decrease the expression of pro-inflammatory marker cyclooxygenase 2 (COX-2), and inhibit cell proliferation, thus suppressing oral carcinogenesis at the cellular level (Mohd Fuad et al., 2023). Probiotics can inhibit the activation of oncogenes by interfering with the nuclear translocation of specific proteins like b-catenin and NF-B, which are crucial for cancer cell survival and proliferation. They have been found to decrease the expression levels of proinflammatory cytokines such as IL-6, IL-1b, and TNF-a, which are associated with cancer progression and inflammation (Badgeley et al., 2021). Through these cellular mechanisms, the probiotics strengthen the immune system and suppress cancer (Fig. 2).

Probiotics: exploring the basics and types of probiotics

Probiotics are live microorganisms that provide several health benefits when consumed in adequate amounts. They are available in both dairy (yogurt, kefir, kumis) and nondairy forms (kombucha, kimchi, miso, tempeh). The most common probiotics include strains of *Lactobacillus* and *Bifidobacterium. Lactobacillus* species include *L. bulgaricus, L. acidophilus, L. casei, L. rhamnosus* and *L.pantarum.* These bacterial strains are acid-tolerant in the acidic environment of the stomach and adhere well to the cells of the intestine (Stavropoulou, and Bezirtzoglou, 2020). Bifidobacterium probiotics include *B. bifidum*, *B. lactis,* B. *longum, Streptococcus thermophilus*, *Pediococcus*, and *Bacilli,* and yeasts such as *Saccharomyces* are also considered probiotics (Stavropoulou, and Bezirtzoglou, 2020). Probiotics are capable of adhering to the gastrointestinal tract and thus are not passed through waste. They can multiply and regulate the immune system of the host. Each strain of probiotic microbe has a unique mechanism of action. They produce antimicrobial substances (organic acids, bacteriocins, hydrogen peroxides) and do not allow pathogenic compounds to adhere to the GI tract, starve pathogens from nutrient sources, and enhance the barrier function of the intestine (Ashaolu, 2020). The antimicrobial compounds produced by probiotics target pathogenic cells by inhibiting cell wall synthesis and pore formation. The lactic acid and acetic acid produced by probiotic microbes inhibit the growth of pathogenic *Salmonella* species (Ashaolu, 2020). Probiotics have several effects on the human body, including the synthesis of vitamins, the metabolism of bile salts, the neutralization of cancer cells, the production of acids and short-chain

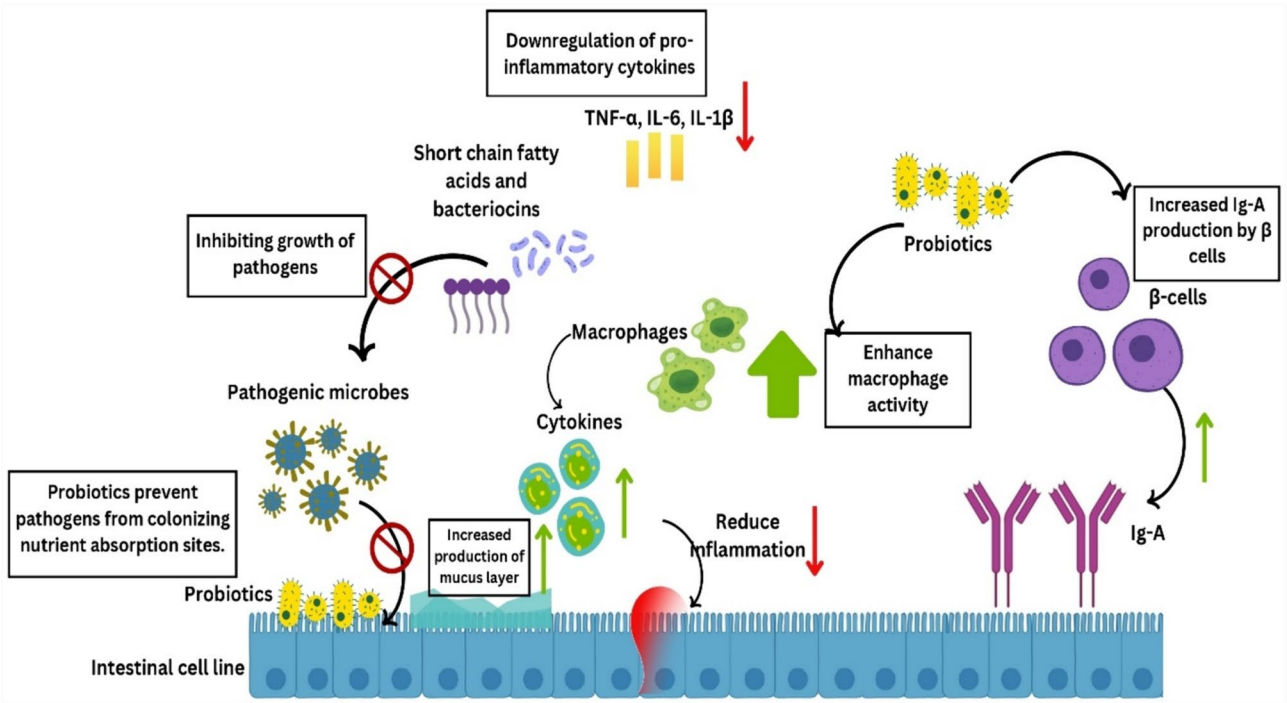


Fig. 2 Cellular mechanisms of probiotics' immunomodulatory effects against cancer

fatty acids, and the exclusion of pathogens by competition, among others. These properties have been found in several probiotic studies. The sources of probiotic foods are nutrient-rich foods such as grains, milk, and legumes, which are excellent sources of carbohydrates, proteins, vitamins, and minerals. In some fermented foods, such as yogurt, the fermentation process is initiated by the addition of a specific strain of microorganisms called the starter culture. In other foods such as sauerkraut, there is not a specific strain, but wild or indigenous microorganisms are present. The health-imparting properties of particular strains of microbes have been proven by clinical trials. For example, yogurt consumption was associated with a reduction in the development of metabolic syndrome in older adults, a reduced risk of weight gain, and improved digestion in lactose-intolerant individuals. Studies have also revealed that the association between consuming yogurt and soy milk decreases the likelihood of developing cardiovascular diseases (Sanders et al., 2018). A daily study of adults in Korea who consumed high amounts of other probiotic kimchi showed a reduced occurrence of the skin disease atopic dermatitis (Kim et al., 2017). The intake of fermented soy products such as miso and natto reduces the risk of hypertension (Nozue et al., 2017). The various probiotics and associated foods that help to manage cancers have been given in Table 1.

Probiotic foods and their role in cancer management

Probiotic foods, having beneficial live microorganisms, play a crucial role in cancer management by modulating the immune system, enhancing gut microbiota diversity, producing anticancer metabolites, and reducing inflammation. These actions collectively help inhibit cancer cell growth and improve the overall immune response, contributing to better cancer prevention and treatment outcomes. The anticancer properties of probiotic foods are shown in Fig. 3.

Yogurt

Yogurt is a probiotic, milk-based product formed by the fermentation of milk by lactic acid bacteria. It is a nutrient-dense product that provides numerous health benefits to consumers. The dominant bacterial species in yogurt include *Lactobacillus bulgaricus, Streptococcus thermophilus, Lactobacillus acidophilus, Lactobacillus rhamnosus, Lactobacillus casei, Bifidobacterium lactis,* and *Bifidobacterium bifidum* (Nyanzi et al., 2021). The production of lactic acid by the fermentation of lactose results in a reduction in pH. This prevents the growth of foodborne pathogens, as a reduction in pH creates a harsh environment unsuitable for their growth (Kamal et al., 2018). Fermentation also leads to a reduction in lactose content and makes yogurt an excellent choice for people who are lactose intolerant (Moineau-Jean

Table 1 Probiotics in the management of various cancers

Probiotic food	Probiotics	Effects	References
Yogurt	*Lactobacillus bulgaricus, Streptococcus thermophilus*	Lower risk of Nonalcoholic Fatty Liver Disease	Zhang et al. (2020)
Kefir	*Lactobacillus* species, *Saccharomyces cerevisiae*	Obesity management by reduction in serum zonulin levels, glucose and High- density lipoprotein	Pražnikar et al. (2020)
Sauerkraut	*Leuconostocmesenteroides, Lactobacillus plantarum* and *Lactobacillus brevis*	Antioxidant, anti-inflammatory and anticarcinogenic properties	Peñas et al. (2017)
Kombucha	*Bacillus coagulans, Lactobacillus species* and*Gluconobacter*	Antioxidant, anti-carcinogenic properties, aids in cardiovascular disease management and hypoglycemic activity	Selvaraj and Gurumurthy (2022)
Miso	*Aspergillus oryzae*	Reduced occurrence of cardiovascular diseases and hypertension	Ito (2020)
Buttermilk	*Lactococcus lactis, Lactobacillus casei, Lactobacillus acidophilus*	Antidiabetic, Anticancer, and Cholesterol-lowering	Bhukya and Bhukya (2022)
Kimchi	*Leuconostoc, Lactobacillus, and Weissella*	Anticancer properties	Lee et al. (2023)
Natto	*Bacillus subtilis*	Anticarcinogenic, antibacterial, immunity boosting, anti-inflammatory	Afzaal et al. (2022)
Hawaijar	*Bacillus species*	Anticancer, anti-diabetic, hypocholesterolaemia	Premarani and Chhetry (2011)
Fermented Bamboo shoots	*Lactobacillus species*	Anticancer, antioxidant, anti-aging, antimicrobial	Behara and Balaji (2021)

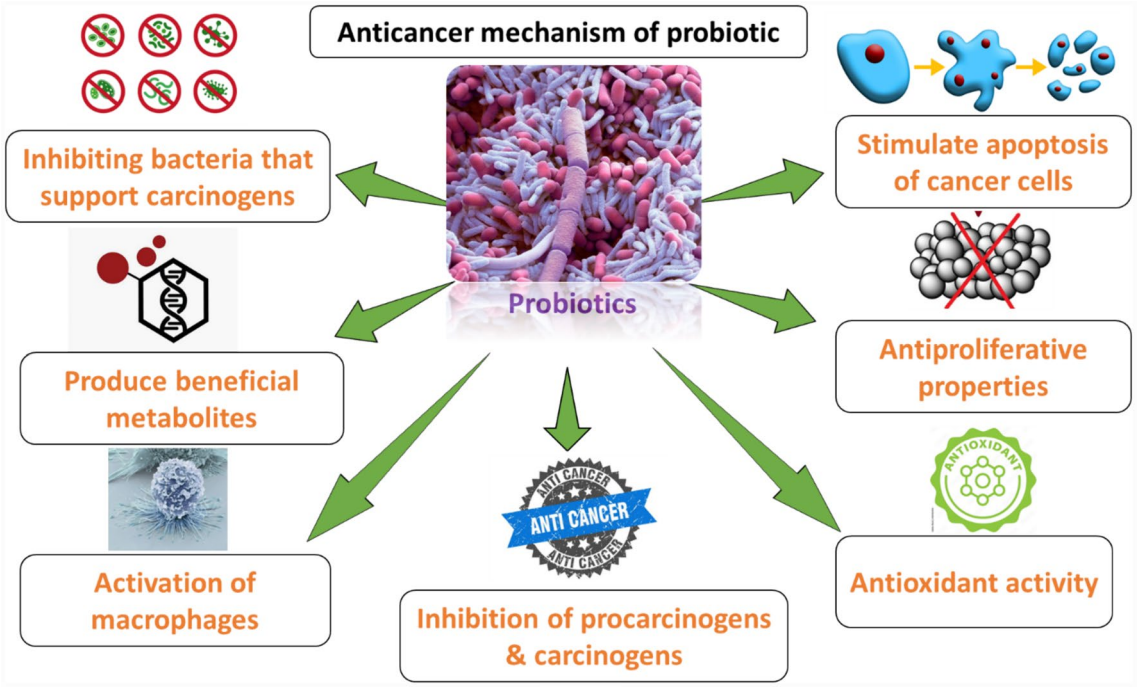


Fig. 3 The anticancer properties of probiotic foods

et al., 2019). Yogurt has bioactive peptides that impart antioxidant activities (Ali et al., 2022). The consumption of yogurt has been linked to a reduced risk of colorectal cancer. The gut microbiome is a major factor affecting the risk of cancer development. A healthy gut microbiome prevents the formation of tumors in the intestinal tract. A detailed analysis of studies on yogurt intake and its effect on colorectal cancer was performed by Sun et al. (2022). Sixteen studies including 1,129,035 people were analyzed. The high consumption of yogurt by the test participants decreased the possibility of developing colorectal cancer. Yogurt helps in the formation of short-chain fatty acids, which modulate the immune system, prevention of pathogenic compound entry into the intestinal epithelium, and antimicrobial compound production. It also lowers the activity of fecal enzymes (nitroreductase, b-glucuronidase, and azoreductase), which are responsible for the formation of carcinogens from procarcinogens in the colon. Another study on dietary fiber and yogurt consumption and its association with lung cancer was performed by Yang et al. (2020). The study showed a reduction in the risk of lung cancer in test patients with proper lifestyle habits, including the intake of dietary fibers along with yogurt. More than 1.44 million individuals were considered for this study. A total of 15 to 19% of individuals who consumed large amounts of yogurt had a positive effect on the incidence of lung cancer. In addition to yogurt, the intake of dietary fiber reduced the risk of lung cancer by 39%. Yogurt has anti-inflammatory properties that help individuals with inflammation from squamous cell carcinoma, alcohol intake, and lung carcinogenesis. Research has suggested that the colonization of the intestinal tract by probiotic species such as *Lactobacillus* and *Bifidobacterium* improves the gut microbiome and positively affects the physical health of individuals (Yang et al., 2020). Figure 4 shows some of the bioactive compounds synthesized by microorganisms found in different fermented foods.

Kefir

Kefir is a popular fermented drink with an acidic and bubbly taste profile produced by the fermentation and carbonation of kefir grains. It can be milk or water based. It has become popular among consumers worldwide because of the many health benefits it provides. Kefir is slightly different from the other fermented foods because of the specific property of its starter, kefir grains. These bacteria are whitish to yellow and are composed of exopolysaccharides kefiran and proteins along with a symbiotic association of lactic acid bacteria, acetic acid bacteria, and yeasts (Garofalo et al., 2020). The dominant bacterial species in kefir include *Lactobacillus para-casei, Lactobacillus kefiranofaciens, Lactobacillus plantarum, Lactobacillus bulgaricus* and *Lactobacillus acidophilus.* The dominant yeast species included *Saccharomyces unisporus, Saccharomyces cerevisiae, Kluyveromyces marxianus,* and

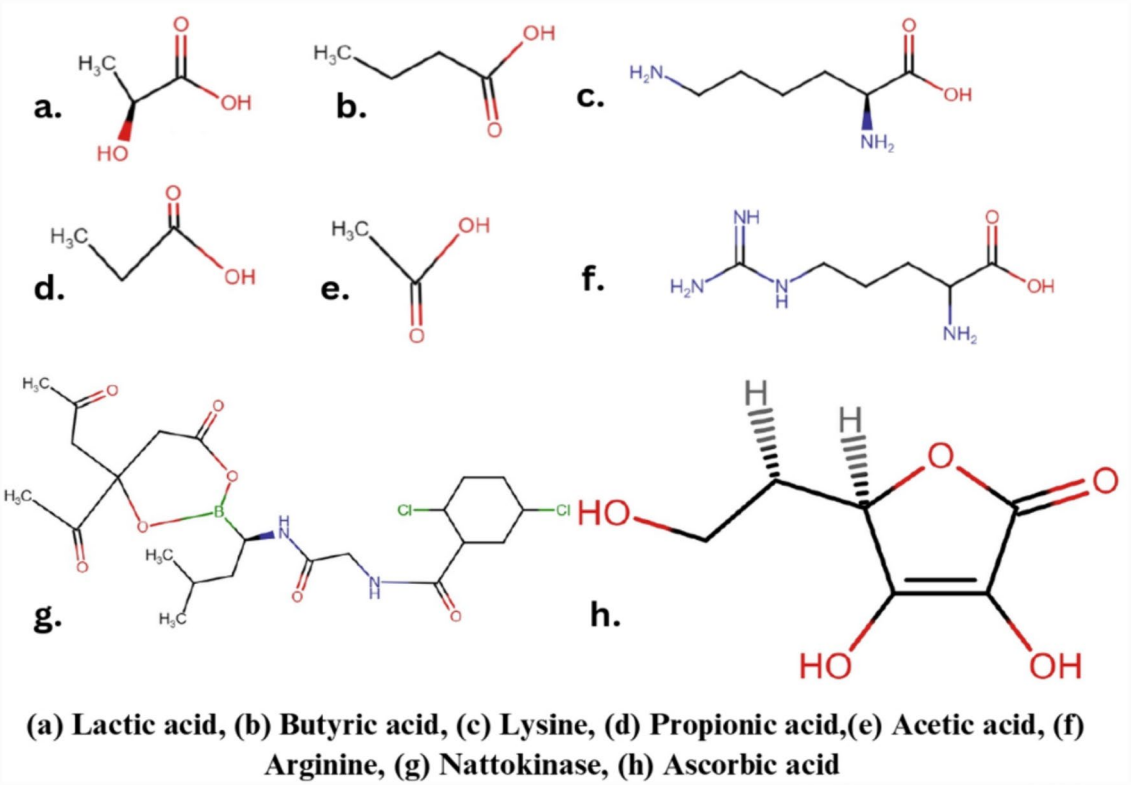


Fig. 4 Some bioactive compounds synthesized by microorganisms found in fermented food

Candida kefyr. Kefir consumption has been associated with valuable health benefits, such as anti-diabetic, anti-inflammatory, antimicrobial, anticarcinogenic, and antitumor effects. These properties are attributed to the several microbes present in kefir, the metabolites they produce, and the exopolysaccharide kefiran present in kefir (Wyk, 2019). Fermentation products include acetic acid, lactic acid, essential amino acids, vitamins, folic acid, bioactive peptides, and other nutraceutical metabolites (Garofalo et al., 2020). Kefir has anticancer effects because of its ability to retard tumor growth, modulate the gastrointestinal microbiota, decrease DNA damage, and inhibit the spread and activation of procarcinogens (Sharifi et al., 2017). The anticancer effects of kefir have been studied and reported in various types of cancer, such as blood cancer, breast cancer, colorectal and gastric cancer, and tumors. Kefir had apoptotic, antioxidant, and antiproliferative effects on the human melanoma cell line HMV-1/SK-MEL, the human mammary cancer cell line MCF-7, the human T-cell leukemia cell line HuT-102, the gastric cancer cell line SGC7901, the colorectal cell line Caco-2/HT-29, and the colon cancer cell line. These studies were performed in vivo and in vitro among various test organisms, including humans and mice (Azizi et al., 2021).

Sauerkraut

Sauerkraut is a widely consumed traditional Chinese fermented food with a distinctive sour flavor. It is also popular in the northeastern regions of India. It is an excellent source of probiotics, minerals, and organic acids. Sauerkraut provides several health benefits to consumers, including anti-inflammatory, antioxidant, anticancer and antiobesity effects (Lavefve et al., 2019). It is produced by placing cabbage leaves in a brine solution having 0.5 to 3.5% salt. The microbes that cause fermentation include lactic acid bacteria, Enterobacteriaceae, Pseudomonadaceae, and yeast species. The salt concentration is the governing factor of fermentation and the taste and quality of the final product. A suitable concentration of salt inhibits the growth of pathogenic microorganisms and favors the proper growth of lactic acid bacteria (Pérez-Díaz et al., 2020). Sauerkraut is known to have anticancer properties. This is because of the chemical compound glucosinolates. These compounds are sulfur-containing phytochemicals with a β-D glucose unit and an aliphatic amino acid-derived side chain. It can protect the body against the development of cancer. Isothiocyanates and indoles are produced upon the breakdown of glucosinates. These compounds lower cancer risk by activating genes

that suppress tumors, slow tumor growth, and increase the self-destruction of cancer cells. Glucosinates stimulate enzymes that are responsible for the deactivation of carcinogens and decrease the ability of cancer cells to spread (Zawadzki, 2023). *Bacillus* lipopeptide-iturin A-2, a metabolite produced by *Bacillus velezensis*strainT701, was isolated from sauerkraut. It showed antitumor and cytotoxic effects on the breast tumor cell line BT474 and cytotoxic effects on the cervical cancer cell lines HeLa and MCF-7 (Jiang et al., 2021).

Kombucha

Kombucha is a probiotic beverage produced by the fermentation of black tea dissolved in sugar by SCOBY, a symbiotic culture of bacteria and yeast. SCOBY is a bell-shaped, spongy, textured culture commonly known as tea fungus. Freshly fermented Kombucha fruits have a sweet taste like that of apple cider fruits, whereas prolonged fermentation leads to the formation of acidic flavors similar to those of vinegar. The bacterial strains and yeasts found in Kombucha include *Acetobacter aceti, Gluconacetobacter xylinus, Acetobacter xylinoides, Acetobacter pasteurianus, Sachharomycodes ludwigii, Saccharomyces cerevisiae, Torulaspora, Pichia* and *Candida*. The combined action of yeasts and bacteria on tea results in the formation of several bioactive compounds that have health-enhancing potential (Dutta and Paul, 2019). Several studies on the anticancer action of Kombucha have been performed and have shown positive results. Kaewkod et al., 2022, investigated the effect of traditional kombucha combined with other medicinal plants and its anticancer effect on colorectal cancer cells. Kombucha was prepared with black tea and additional extracts of *Aegle marmelos* and *Terminalia catappa*. MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide) studies were conducted on Caco-2 colorectal cancer cells. DNA damage and apoptosis in cancer cells after treatment with the enhanced Kombucha extracts were detected using a terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) assay. All the treated samples showed DNA damage during the later stages of apoptosis and cell cytotoxicity to Caco-2 cancer cells. Kombucha showed enhanced anticancer activity along with doxorubicin against the colorectal cell line HCT-116. Kombucha extracts are capable of 1.2 times earlier induction of apoptosis and a twofold increase in G_0 and G_1 phase arrest (Rasouli et al., 2021). The anticancer potential of kombucha is linked to the presence of dimethyl 2-(2-hydroxy-2-methoxypropilidine) malonate, a compound that can suppress cancer cells (Taupiqurrohman et al., 2022). The anticancer compound in common probiotics has been given in Table 2.

Miso

Miso is a popular traditional fermented food in Japan with a typical savory flavor profile. The production of miso involves a two-stage fermentation in which the first stage involves the development of koji with *Aspergillus oryzae* followed by the addition of koji to a soybean and salt mash. This mixture is then kept for fermentation for the development of the desired taste (Allwood et al., 2021). The color of the miso depends on the duration of fermentation and the amount of salt and koji used. Miso has several bioactive compounds that are responsible for its health-promoting properties. These include vitamins, minerals, phenolic acids (syringic acid and vanillic acid), and isoflavones (genistein and daidzein) (Chan et al., 2021). Isoflavones isolated from miso have shown antiproliferative effects on certain cancer cell lines. Hydroxygenistein showed the highest antiproliferative activity against the promyelocytic leukemia cancer cell line HL-60. It has also been reported that miso has the potential to prevent cancer by enhancing the cytotoxic activity of cancer cells in the spleen and reducing tumor formation (Jung et al., 2006). Miso fermented with *Aspergillus oryzae* and *Bacillus subtilis* has exhibited antiproliferative effects on several human cancer cell lines, including H_EPG2 (liver carcinoma), MCF7 (breast carcinoma), and HCT116 (colon carcinoma). The anticancer activity was due to the presence of more isoflavones in miso than in unfermented soybeans (El-Shenawy et al., 2012). Miso suppressed liver tumors in mice and breast tumors in rats (Watanabe, 2013).

Natto

Natto is a traditional Japanese dish prepared by the fermentation of steamed soybean seeds by *Bacillus subtilis.* It has become popular due to its nutritional profile, which has several health benefits. It has a unique flavor with a sticky and slimy consistency. The health benefits are due to the presence of bioactive compounds and essential nutrients such as soybean isoflavone, natto kinase, γ-polyglutamic acid, biogenic amines, and vitamin K_2. It also has 100 times more menaquinone-7 than most cheeses (Afzaal et al., 2022). Natto kinase extracted from natto treated early subcutaneous breast cancer in mice by encouraging vascular regeneration and inhibition of tumor angiogenesis. FOXM1, a biomarker present in various malignant cancers, promotes the proliferation of cancer stem cells and promotes the renewal of pancreatic cancer cells and the spread of cancer in the liver, stomach, lung, and pancreas. Natto kinase hampers the expression of this transcription factor, thus resulting in cancer management. Another family of enzymes, MMP2, which enhances tumor invasiveness and tumor growth, is reduced by natto kinase. Thus, it has been clearly shown that the bioactive component of natto has the potential to fight

Table 2 Anticancer compounds in common probiotics

Probiotic food	Anticancer compound	Mechanism of action	References
Yogurt	Bioactive peptides (beta-casein and kappa casein fragments (β-CN 135–144,193–209 and κ-CN 18–29,141–146,161–169 fragments)), butyrate, short-chain fatty acids	Inducing apoptosis of cancer cells (negatively charged cancer cells bind to positively charged peptides), rupturing the cancer cell membranes, and causing their death	Nyanzi et al. (2021), Mann et al. (2017)
Kefir	Interferon-β, BAX	Anti-inflammatory, anti-proliferative, and immunomodulatory effects by increasing macrophage production and phagocytosis, decrease the levels of TGF-α, TGF-β, causing initiation of apoptosis, low levels of TGF-α, TGF-β, show antiproliferative effects in cancer cells, apoptosis regulation	Verruck et al. (2019)
Sauerkraut	Isothiocyanates, ascorbigen, ascorbic acid	Decrease cell mutation and prevent oxidative DNA damage, inhibition of pro-inflammatory cytokines	Ciska et al. (2021), Shahbazi et al. (2021)
Kombucha	Glucuronic acid, acetic acid, vitamin C, B_1, B_2, B_{12}, ethyl alcohol, dimethyl malonate, vitexin, DSL (D-saccharic acid-1, 4-lactone)	Antiproliferation activity, antioxidant activity Genetic mutation inhibition, induction of apoptosis, terminating metastasis, hepatoprotective action against toxic liver carcinogens	Villarreal-Soto et al. (2019) Chelho et al. (2020)
Miso	isoflavones (genistein and daidzein) and phenolic acids (syringic and vanillic acid), saponins, lunasin	Estrogen binding activity prevents hormone-related cancer, prevents angiogenesis in tumor masses, prevents the growth of tumor cells, promotes cell apoptosis, and positive regulation of mRNA expression of various tumor-suppressing genes thus inhibiting cell malignancy	Chan et al. (2021) Prado et al. (2022)
Natto	Isoflavones, flavonoids, phytoestroptease inhibitor, phytic acid Natto kinase	Antitumor activity, inhibit expression of transcription factors CD44, CD31, FOXM1, and vimentin which regulate the proliferation of tumors thus reducing the growth rate of tumor	Wang et al. (2023), Yuan et al., (2022)
Kimchi	Nisin, GABA (γ-Aminobutyric Acid), ornithine, mannitol, dextran, 3- Phenyllactic acid, and 2-hydroxyisocaproic acid	Apoptosis, anti-proliferation activity, cell cycle arrest, inhibition of mutagenesis and angiogenesis, oxidative stress modulation	Lee et al. (2021)
Buttermilk	Phospholipids (phosphatidylcholine, phosphatidylinositol, phosphatidylethanolamine), sphingolipids (lactosylceramide, glucosylceramide, and sphingomyelin)	Antiproliferative activity, anti-inflammatory	Ali (2019), Freitas Mascarello et al. (2019)
Hawaijar	Amino acids, minerals	Anticancer properties	Saibhavani et al. (2020)
Fermented bamboo shoots	Sitosterol-3-O-β-d-glucoside	Enhancement of proapoptotic genes (Bax, P53, caspases) and the downregulation of antiapoptotic gene- BCL2	Abdelhameed et al. (2020)

cancer-causing agents (Zhang et al., 2019). Freeze-dried natto water extracts have been shown to remediate melanoma through cytotoxic effects. Autophagy acridine orange staining and flow cytometry assays revealed a shift from autophagy to apoptosis in the melanoma cell lines. Natto extracts also increase oxidative stress in cancer cells and initiate apoptosis by suppressing AMP-activated protein kinase (Chou et al., 2021). Nattokinase extracts were administered to hepatocellular carcinoma-infected mouse models. The results showed a 31% increase in the survival rate of the mice, and ultrasound images revealed a significant reduction in the tumor size. This was also due to the ability of natto kinase to suppress the expression of the cancer biomarkers CD44, CD31, FOXM1, and vimentin. These factors are responsible for the proliferation, drug resistance and survival of various cancers (Yan et al., 2019). A fructose polysaccharide, Levan, which is produced by *Bacillus subtilis* in natto, induces apoptosis in a neuroblastoma cancer cell line (SH-SY5Y) via caspase 3/7 activation (Vieira et al., 2021).

Kimchi

Kimchi is an Asian fermented dish prepared from natural napa cabbage (*Brassica rapa*) or Chinese cabbage by crossbreeding northern Chinese turnip and Bok choy cabbage from China. Kimchi has also been registered at the Codex Alimentarius and received international recognition. It is produced by fermenting cabbages or radishes and additional ingredients such as those in closed containers at low temperatures to allow microbial activity and the development of the desired flavor. Fermenting microbes include *Bacillus subtilis, Bacillus mycoides, Lactobacillus brevis, Lactococcus carnosum, Lactobacillus kimchi, Serratia marcescens, Saccharomyces species, Candida species and Leuconostoc species,* among others (Surya and Lee, 2022). Cancer cachexia is a health condition in patients with advanced cancer that results in skeletal muscle degeneration, weight loss, and adipose tissue loss. Interleukins are the primary mediators of cachexia. Kimchi can modulate and suppress the interleukin-6 (IL-6) response, resulting in the treatment of cancer cachexia. Kimchi intake significantly inhibited muscle degenerating and lipolysis genes, including muscle ring finger protein-1 (MuRF-1), hormone sensitive ligase (HSL), adipose triglyceride lipase (ATGL), and atrogin-1 (An et al., 2019). Kimchi intake can also prevent colitis-related cancer through several mechanisms, such as weakening inflammasomes (IL-18 and caspase-1); inducing anti-proliferative effects through the regulation of BAX, caspase-3 and beta-catenin; enhancing antioxidant effects; and regulating cytoprotective actions. It also induces the tumor suppressor 15-PGDH and inactivates ERK1/2, contributing to cancer prevention (Han et al., 2020). *Weissellacibaria*, found in kimchi, has anticancer properties due to its ability to produce tumor necrosis factors. It has been shown to suppress cancer cell growth in colorectal cancer cells (Ahn et al., 2013). These studies indicate the potential of kimchi as an anticancer food.

Buttermilk

Buttermilk is a byproduct of butter manufacture and is a rich source of various phospholipids, enzymes, glycoproteins, and unsaturated fatty acids. Sphingolipids and glycerophospholipids regulate several metabolic processes (Ferreira et al., 2022). However, bulky sphingomyelin and lactosylceramide inhibited the growth of SW480 colon cancer cells. Buttermilk caused the deactivation of ERK1/2, an enzyme family responsible for the proliferation of human colorectal cancer cells (Kuchta-Noctor et al., 2016). Bacteriocin isolated from *Lactococcus lactis,* a bacterium predominant in buttermilk, has shown anticancer activity against cancer cell lines in breast cancer (MCF-7) and a lymphoid cell line (CCL-119). The results clearly showed the greater toxicity of bacteriocin against cancer cells than against normal cell lines (Abbdul-Kaliq et al., 2020). Lipid fractions isolated from buttermilk were studied for their antiproliferative activity against several cancer cell lines, including skin cancer (U252, HaCaT), breast cancer (MCF7), ovarian cancer (NCI), kidney cancer (786–0), lung cancer (NCI-H460), colon cancer (HT29), and bone marrow cancer (K-562) cell lines. The sphingolipid- and phospholipid-rich fractions were found to have strong antiproliferative effects on the different cancer cell lines studied (Castro-Gomez et al., 2016). The above studies indicate that buttermilk is a rich source of nutritional compounds with anticancer potential.

Hawaijar

Hawaijar is a common traditional fermented soybean food produced by the Manipur. It has a sticky texture. The seeds were soaked in water overnight, washed, and then boiled until soft. After washing with hot water, the boiled seeds are placed in bamboo baskets lined with a layer of fig or banana leaves. The closed basket is then wrapped with jute cloth and buried in a paddy or kept in the sun or near a stove. The fermented hawaijar is ready for consumption within 3 to 4 days. The production of ammonia-like flavors and the development of mucilage indicate good-quality hawaijars (Devi et al., 2013). The functional microorganism *Bacillus* imparts antioxidant and antidiabetic properties to Hawaiju (Singh et al., 2023). It is also a rich source of proteins (Sarkar et al., 2015). It has anti-osteoporosis, anticancer, and hypocholesterolemic effects (Saibhavani et al., 2020). Further research studies need to be performed to fully explore the anticancer potential of hawaijars.

Fermented bamboo shoots

Bamboo shoots are fermented and consumed by tribes in northeast India because of their medicinal value and health benefits. As a storehouse of several microorganisms, they can be used as functional probiotic foods. Several food products based on fermented bamboo shoots include soibum, mesu, soijim, soidon, heccha, ekung, hirring, tabah bam shoot pickle, and soidonmahi. They are rich in mineral content and dietary fiber and low in fat. Fermented bamboo shoots contain certain bioactive compounds, such as flavones and glycosides, which have anticancer, antioxidant, and antiaging effects.*Lactobacillus species (L. plantarum, Brevis, and L. lactis)* are the dominant microorganisms (Behara and Balaji, 2021). These phytosterols are rich sources of phytosterols that have been shown to have anticancer and antitumor effects on lung, ovarian, and breast cancers. The mechanism of action involves enabling the antitumor response, boosting the immune recognition of cancer, and managing hormone-related endocrine tumor growth. Phytosterols inhibit the growth of tumors by inducing apoptosis and slowing the cell cycle progression of cancer cells. Moso bamboo has been utilized for the production of an antitumor agent (Hiromichi, 2007). Phenolic acids in tender bamboo shoots are powerful antioxidants that prevent cancer (Nirmala et al., 2014). A phytochemical study of bamboo shoot skins revealed the presence of sitosterol-3-O-β-d-glucoside, which has cytotoxic effects on MCF-7 cancer cells. It also blocked the progression of these cell lines. This was caused by the increase in the expression of proapoptotic genes (Bax, P53, and caspases) and the decrease in the expression of the antiapoptotic gene BCL2 (Abdelhameed et al., 2020).

Microbial metabolites and their mechanism of action against cancer cell lines

The bioactive compounds produced by probiotic microorganisms play an important role in the metabolic activities of consumers. These include bacteriocins, enterocins, exopolysaccharides, short-chain fatty acids (lactic acid, butyric acid, propionic acid, and acetic acid), amino acids (arginine, tryptophan, and tyrosine), vitamins (folate, thiamin, riboflavin, pyridoxine, vitamin B12), and enzymes (amylase,β-galactosidase, superoxide dismutase, and catalase) (Indira et al., 2019). A study on the characterization of exopolysaccharides synthesized by *Lactobacillus plantarum* RJF4 revealed its cytotoxic and proliferative effect on the MiPaCa-2 pancreatic cancer cell line. MTT assays revealed that exopolysaccharides had no inhibitory effects on the normal L6 and L929 fibroblast cell lines, indicating that foods fermented by *Lactobacillus plantarum* RJF_4 are safe for consumption. The Alamar Blue assay depicted the antiproliferative effect of the EPS extracts on pancreatic cancer cells (in a dose-dependent manner, with the highest concentration being 1 mg/ml) (Dilna et al., 2015).

Turin A, a bioactive compound produced by *Bacillus subtilis,* showed anticancer activity on the HepG2 hepatoma cell line. 2-D and 3-D cell culture models were used to study the anticancer effects of these compounds. Compared with 2-D culture at a concentration of 11.91 µM, 3-D culture at a concentration of 55.26 µM had a much greater 50% inhibitory effect. Autophagy, apoptosis, reactive oxygen species accumulation, high expression of apoptotic proteins, and caspase activation were detected in both cell lines (Zhao et al., 2019). The antiproliferative effect of short-chain fatty acids on the colorectal cancer cell line DLD-1 through gene expression inhibition was studied. Acetic acid, butyric acid, and isobutyric acid inhibited DLD-1 cell proliferation. The expression levels of cell proliferation and DNA replication genes were reduced by ≥ 50% after treatment with butyric acid. Among the tested fatty acids, butyric acid had the strongest antitumor activity. Short-chain fatty acids also suppress the metabolic functions of tumors, such as DNA replication, repair, and recombination. All these actions lead to the death of tumor cells (Ohara and Mori, 2019). Another study investigated the anticancer effects of nisin, a bacteriocin produced by *Lactobacillus* species, on several cancer cell lines, such as SW48, LS180, Caco2, and HT29. Nisin (40–50 IU/ml) suppressed the proliferation of LS180 cells. A higher concentration of nisin (250–350 IU/ml) suppressed the proliferation of the Caco2, HT29 and SW48 cell lines. Nisin also downregulates the expression of the metastasis-promoting genes MMP2F, MMP9F, CEAM6, and CEA (Norouzi et al., 2018). Pistachio milk fermented *by Streptococcus, Lactobacillus,* and *Bifidobacterium species* has a large amount of acetate, as it is rich in proteins and fats. This acetate-rich fermented milk has apoptotic and cytotoxic activities against Caco-2 colon carcinoma cells. This is caused by nuclear damage and disruption of microtubules by the caspase-3 protein. Fermented pistachio milk at concentrations of 1%, 2.5%, and 5% had cytotoxic effects on 78%, 56%, and 29% of Caco-2 cells, respectively. Additionally, 5% fermented pistachio milk caused a sixfold increase in early and late apoptosis (Lim et al., 2023). The exopolysaccharide MSR101 EPS (400 µg/ml), which is produced from *Lactobacillus kefiri,* showed 44.1% anticancer activity against HT-29 colon cancer cells. It also caused upregulation of the expression of cancer suppressor factors, including BAX, Cyto-c, BAD, and caspases 3, 8, and 9, and downregulation of the proapoptotic BCl-2 gene, leading to the death of cancer cells (Rajoka et al., 2019).

Challenges

Although several studies have supported the use of probiotics as an adjunct to cancer therapy, many challenges remain to be managed. These differences arise due to variability in the response of individual patients to the probiotic dose, as a strain that is beneficial to one patient might cause a negative reaction in another patient. Deciding and standardizing an optimal dose, timing, and specific strain is a complex task. Moreover, advanced studies must be performed to understand the impact of probiotics on the cancer microenvironment, interactions with chemotherapeutic drugs, and safety. Balancing the positives and the negatives becomes a significant obstacle in utilizing the full potential of probiotic foods as adjunct therapy to cancer treatment.

Future perspectives

Probiotic foods, which are rich sources of nutritional and bioactive compounds, have appeared as potential anticancer agents. The intestinal microbiome plays a significant role in the regulation and suppression of cancer-causing factors. An improper diet, the consumption of processed foods, the intake of alcohol, smoking, and a sedentary lifestyle contribute to an imbalance in intestinal homeostasis. Compared with pathogenic microbes, probiotics modulate this microbiota and maintain the balance of good microbes. The dominant microbes found in all the probiotic foods included *Lactococcus, Lactobacillus, Enterococcus, Streptococcus, and Bifidobacterium* species. Several studies conducted on different types of cancers have supported the tumor-suppressive, antiproliferative, anti-inflammatory, and apoptosis-inducing effects of probiotic foods. These properties are due to the presence of specific compounds produced by different microbes during fermentation of the raw materials. The intake of probiotic foods in addition to a healthy lifestyle can result in the prevention and management of cancer and its negative effects on human health. Advanced clinical trials should be conducted to fully determine the potential of probiotic foods as alternatives to usual cancer therapy. Patients prefer natural treatments rather than treatments based on the use of chemical drugs along with the long-term side effects associated with each medicine. This has led to increased demand for and expansion of the probiotic market. Research studies performed on human and animal models have yielded positive results. For the commercialization and use of probiotics as an alternative treatment to cancer therapy, accurate information on the types of strains used, the dose to be administered and the period for consumption should be obtained. Most people are not aware of the scientific mechanism behind the health-implementing properties of probiotic foods. However, medicinal claims are not mentioned in most marketed probiotic foods. Product labeling and regulatory issues related to the marketing and commercialization of probiotic foods have become a matter of discussion. A unique label showing the health claims of each probiotic can help in its better understanding and utilization. Advanced molecular-level technologies will further help in understanding the complex action of specific compounds that play a pivotal role in anticancer activities. People have become aware of the link between health and diet. This has led to an increase in clinical studies on the use of probiotics not only as alternative treatments but also as potential agents for minimizing the side effects of traditional treatments and reducing and preventing chronic diseases such as cancer. The current market for probiotics is expected to grow as consumers are looking for food items that are not only palatable but also a source of health-improving components. The target audience includes scientists and researchers, doctors, directors of food companies, and the general public looking for healthier options. The high costs of cancer treatments and their long-term side effects have increased the economic and emotional burden on patients. The majority of deaths occur in lower- and middle-class income populations that fail to receive proper and timely medical treatment. Fermented foods can be easily prepared at low cost and have a high concentration of probiotics for the treatment of cancer. All the above findings indicate the potential of probiotic foods to emerge as powerful remedies for several cancers.

This review highlighted the basic mechanism of cancer and how probiotics regulate cancer via specific mechanisms of action. Cancer is still one of the leading causes of death worldwide. It is caused by the abnormal activity of cells, which first causes tumors to develop through uncontrolled growth and then leads to the spread of those cancerous cells to other vital organs. Lung cancer, colon cancer, and breast cancer are the most prevalent types of cancer. Cell proliferation, escape from apoptosis, dysregulation of microRNAs, inflammation, and ingestion of noncancerous cells are the mechanisms responsible for the spread and development of cancer. There is still no proper and complete treatment for cancer. Chemical treatments combined with surgical operations and radiation therapy are used to treat cancer patients. Diet plays an important role in fighting chronic diseases. Recent studies have focused on the use of probiotic foods as alternative therapies for cancer management. Microorganisms and the bioactive nutritional compounds they synthesize have been shown to have anticancer effects on several cancer cell lines. The most popular and health-packed

probiotic foods include yogurt, kefir, sauerkraut, tempeh, kimchi, miso, kombucha, pickles, buttermilk, and natto. Each of these is prepared by fermentation by a specific strain of microorganism. The microbial species that are dominant in most probiotic foods include *Lactobacillus, Bifidobacterium, Streptococcus, Bacillus* and *Saccharomyces* species. They produce specific substances such as organic acids, enzymes, vitamins, and bioactive compounds that are responsible for anticancer mechanisms. Lactic acid and short-chain fatty acid production in yogurt, exopolysaccharide kefiran and interferon-β in kefir, glucosinolates, ascorbigen in sauerkraut, glucuronic acid in kombucha, isoflavones in miso and natto, nisin in kimchi and phospholipids in buttermilk are among the unique compounds developed by microbes. They have shown positive results in studies against various cancers, such as lung cancers, the human T-cell leukemia cell line HuT-102, the human mammary cancer cell line MCF-7, the breast tumor cell line BT474, the colorectal cell line HCT-116, and the colon cancer cell line SW480, among others. The mechanisms involved the induction of apoptosis, anti-inflammatory activity, rupturing of cancer cell membranes, anti-proliferative activity, increased phagocytosis, decreased cell mutation, prevention of oxidative DNA damage and inactivation of cancer-promoting genes. Based on these studies, it can be concluded that probiotic-rich fermented foods can play a major role in the management, reduction, and prevention of several types of cancers.

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REVIEW

A systematic review of potential bioactive compounds from *Saccharomyces cerevisiae*: exploring their applications in health promotion and food development

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Abstract

The ubiquitous yeast *Saccharomyces cerevisiae* (SC), found in wine, beer, and bread, harbors a rich reservoir of bioactive substances capable of significantly improving health and transforming the food industry. In exploring the unexplored potential of SC, this systematic review finds 13 different bioactive compounds (BACs) that this yeast produces. We examine their wide variety of health advantages and explored 13 potential functions, from promoting gut and immune system health to preventing chronic illness. Environmentally beneficial methods are promoted via SC fermentation, which uses a readily available and renewable material. Furthermore, the bioactive compounds that have been identified can be utilized to create novel functional foods that meet the increasing needs of consumers who seek out items that provide health advantages beyond simple nutrition. The review also looks into SC's amazing adaptability, showing how it can be used to ferment an astonishing more than thirteen different food products. This emphasizes how SC has the ability to transform the food sector in a sustainable manner. The transformative potential of these BACs in food development goes beyond the domain, revolutionizing the food industry, and leading to a healthier planet and a tastier palate. This review serves as a conduit for bridging the gap between the science community and the industry, facilitating the realization of the enormous potential of SC's BACs within the food and healthcare sectors. It clears the path for further study and development and encourages the development of new functional foods and nutraceuticals that make use of this ordinary yet extraordinary yeast.

Applications of bioactive compounds produced by *Saccharomyces cerevisiae* for health and food industry

Highlights

- Explored wide spectrum of *Saccharomyces cerevisiae* (SC)-derived bioactive compounds (BAC).

Balaji Doolam and Bishwambhar Mishra contributed equally to this work.

Extended author information available on the last page of the article

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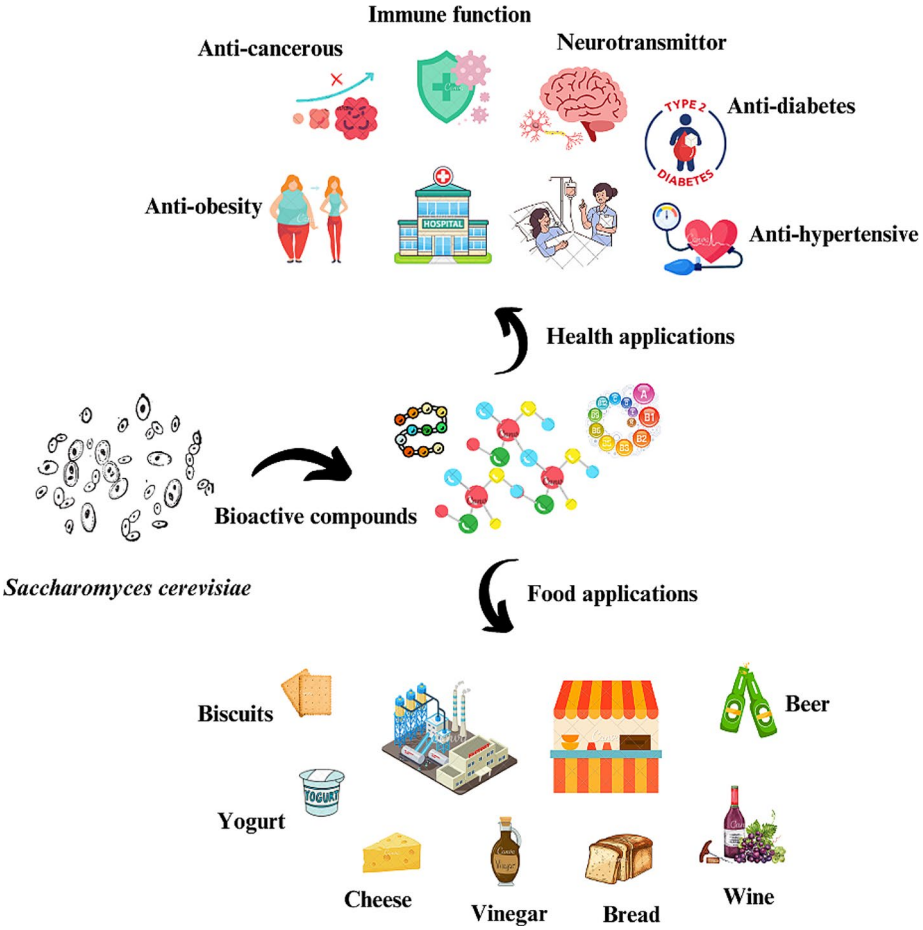
- Outline applications in functional foods and their established health benefits through a systematic review.
- Highlight the transformative potential of these bioactive substances in revolutionizing food production.
- Bridging the gap between the scientific community and industry for SC as functional foods.

Graphical Abstract



Keywords *Saccharomyces cerevisiae* · Yeast · Bioactive compounds · Health benefits · Functional foods · Food industry · Sustainability

1 Introduction

Saccharomyces cerevisiae (SC) is a type of yeast, a single-celled fungal microbe, often known as baker's or brewer's yeast. From ancient times, the species has played a significant role in baking, brewing, and winemaking. It is said to have been isolated from grape skin at first. Much like *Escherichia coli*, the model bacterium, it is one of the most extensively studied eukaryotic model organisms in molecular and cell biology. It is the microbe responsible for the most prevalent kind of fermentation. The diameter of SC cells ranges from 5 to 10 μm, and they are ovoid to spherical in shape. It reproduces through budding (Feldmann, 2012). For over 5,000 years, the history of yeast has been intertwined with the development of bread, beer, and wine, some of the world's most popular food and beverage commodities. The microbiological science of these products began in the mid-1600s, with Antonie van Leeuwenhoek (The Netherlands) reporting the first observations of yeast cells. Yeasts' influence in food and beverage production transcends iconic ferments like bread, beer, and wine, playing a vital role across countless industries. Some yeasts have potent antimicrobial properties, making them valuable in the biocontrol of food deterioration. Their probiotic action is also becoming more popular. On the other hand, yeasts can also cause spoiling, resulting in financial losses, and their public health relevance in foods and beverages is an increasing issue (Fleet, 2006).

Due to its widespread application in food and beverage fermentation, where it holds significant commercial value, SC has been a vital part of human civilization. Approximately 30% of the one million tonnes of yeast generated annually in the European sector is exported worldwide. From 2013 to 2018, the yearly growth rate of the global market was 8.8%. Regarding the beverage industry, SC is involved in the production of numerous fermented beverages, like wine, beer, and cider; distilled beverages, like rum, vodka, whisky, brandy, and sake; additionally, it is involved in the production of other alcoholic beverages worldwide, derived from fruits, honey, and tea (Parapouli et al., 2020).

SC has emerged as a promising and sustainable approach for the production of bioactive compounds (BAC) with significant implications for human health and food development. Waste management is quickly shifting to waste valorization, with biological and chemical refining methods leading the way (Marousek et al., 2024). Faria et al., 2023 demonstrated the upcycling potential of SC, transforming food waste into valuable sources of BACs. This not only reduces the environmental impact but also creates opportunities for novel functional food ingredients. Darwesh et al., 2023 explored SC fermentation to enhance the health benefits of cinnamon. Their study revealed a significant increase in antioxidants and other BACs with potential anti-inflammatory and antimicrobial properties. This study paves the way for SC-fermented functional foods with improved health profiles. Tadioto et al., 2023 further emphasize the versatility of SC, highlighting its ability to produce a wide range of BACs from simple substrates. This bioconversion process not only promotes human health by creating novel ingredients but also fosters environmental sustainability by reducing reliance on resource-intensive extraction methods. Additionally, Ballet et al., 2023 underscore the broader "One Health" impact of SC; stating that SC-mediated production of BACs presents a compelling and sustainable approach for advancements in human health and food development. This aligns with the principles of responsible consumption and production, good health and well-being, and sustainable cities and communities, as outlined in

Sustainable Development Goals. The eco-friendly and versatile nature of SC positions them as key players in shaping a healthier and more sustainable future for food and human health.

Beyond its well-known function in fermentation, SC's adaptability includes improving the sensory attributes and nutritional profile of a wide variety of food products. Y. Li et al.'s studies from 2022 demonstrate how SC-derived GABA in cheese may affect neurological and psychological processes, providing new opportunities to investigate the relationship between nutrition, neurotransmitters, and mental health. Likewise, studies have demonstrated that including SC into the fermentation process of tea and coffee enhances their bioactive and flavor characteristics (Majumder et al., 2022; Kim et al., 2022). In addition to improving the biscuits' flavor and texture, the fermentation of soybean flour with SC raises the amount of dietary fiber, protein, ash, and minerals (barreto et al., 2022). Yogurt's structure, texture, and possibly even health benefits can be enhanced by adding β-glucans from yeast (Santos et al., 2019). Beyond these examples, SC is used in the fermentation of a variety of food products, including milk kefir (Hong et al., 2019) and sprouts (Chen et al., 2020). Qiao et al. (2022) report that β-glucan, a polysaccharide present in the cell wall of yeast, has demonstrated potent anti-inflammatory properties. Neurotransmitter GABA, which is generated by SC, provides insight into a possible connection between this common yeast and brain function (Yılmaz & Gökmen, 2018). Moreover, studies indicate that peptide-rich wasted yeast extract extracts exhibit strong antioxidant properties, which could make them useful allies in the fight against oxidative stress (Oliveira et al., 2023). Research indicating that wines fermented with particular strains of SC can lower vascular inflammation supports these findings further (Grieco, Giovinazzo, and Carluccio, 2019). The historical development and attained mile stone of *Saccharomyces cerevisiae* from ancient fermentation practices to modern biotechnological applications have been illustrated in Fig. 1.

This systematic review seeks to critically evaluate the existing knowledge on SC-derived BAC for health and food applications, with a specific focus on the identification and categorization of these compounds. Utilizing state-of-the-art analytical techniques and methodologies, we aim to unravel the full spectrum of bioactive potential within SC. However, a comprehensive understanding of how to integrate these BACs into functional food development practices remains a challenge. This systematic review aims to bridge this gap by

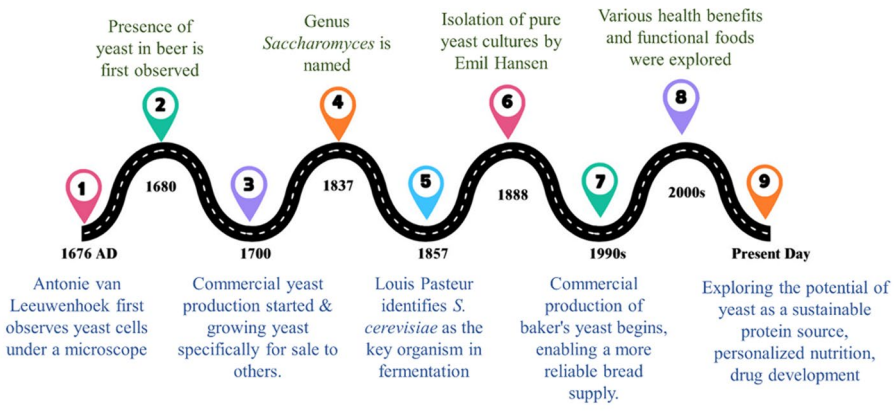


Fig. 1 A timeline illustrating the historical development of *Saccharomyces cerevisiae* from ancient fermentation practices to modern biotechnological applications

examining the functionality of SC-derived BACs as natural food additives and contributors to overall nutritional quality. By drawing connections between microbiology, biotechnology, nutrition, and health sciences, we provide a holistic understanding of SC's impact on both human health and the food industry. This integrative approach not only contributes to our understanding of BACs but also guides future research endeavors and developments in the field.

2 Methodology

As a result, a systematic review of the literature was performed. To ensure scientific quality and reduce the potential of bias, adherence to the PRISMA Statement methodology (Moher et al., 2009) was maintained in the study design. The Scopus database was utilized for conducting a comprehensive literature search for papers relevant to this review from 2015 to September 9, 2023. A network map (Fig. 2) was created using VOSviewer software to show the links between the BACs produced from SC and their possible uses. Insightful information about the complex relationships between different BACs and their benefits to food or health is offered by this network analysis. Clear groupings of substances linked to particular advantages, including antioxidant or anti-inflammatory properties, are shown by the map. The visual representation of SC-derived BACs and their potential for further study and development is better understood with the help of this visual representation.

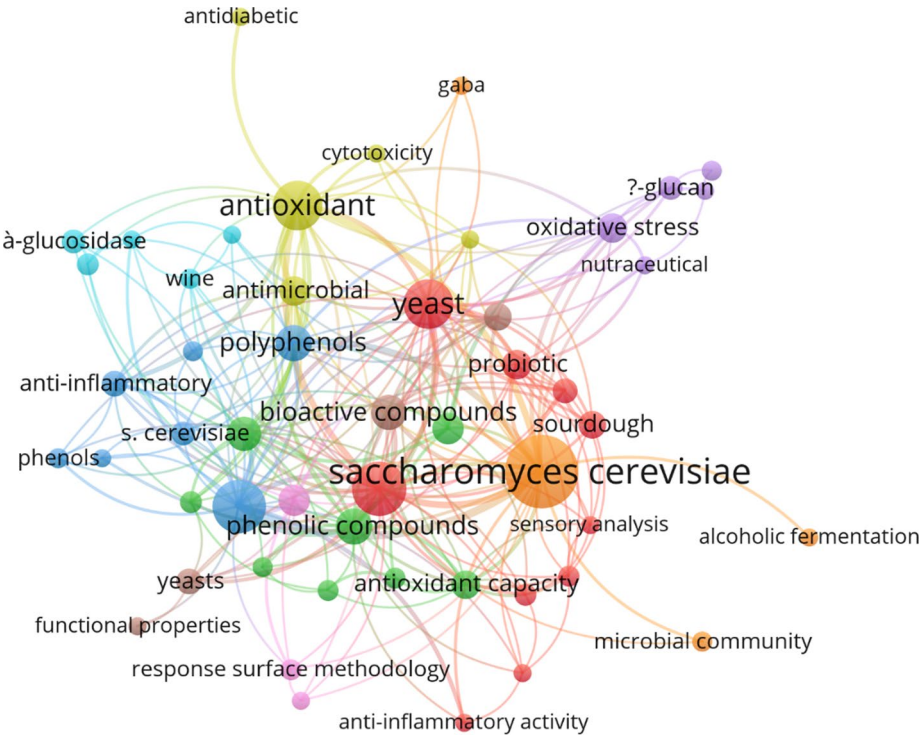


Fig. 2 Exploring the potential of SC: A network analysis of bioactive compounds and their applications

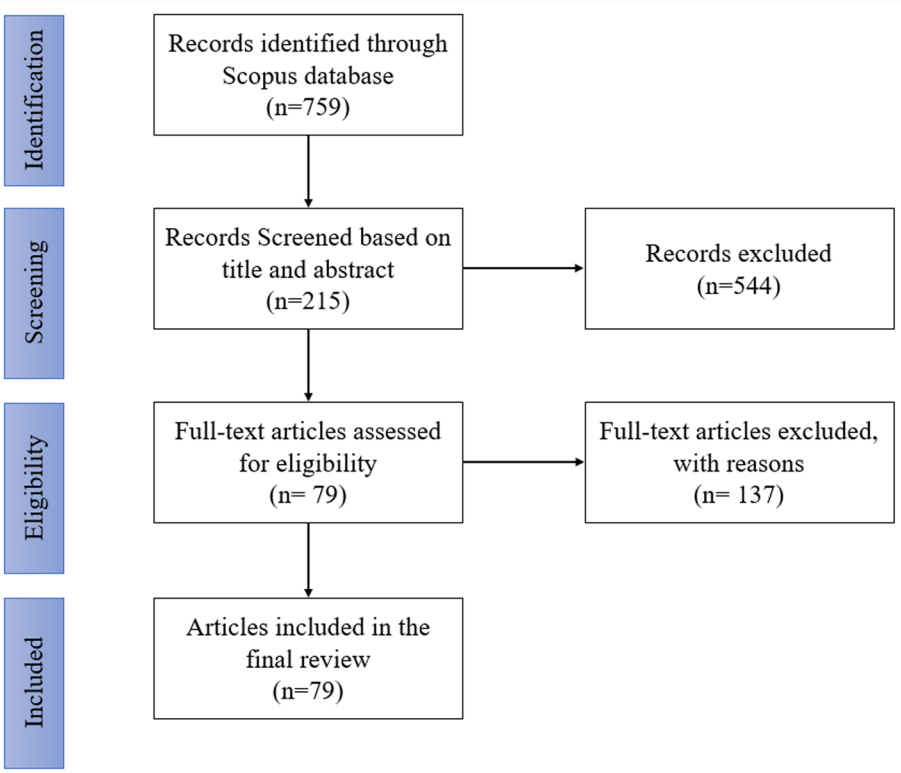


Fig. 3 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram

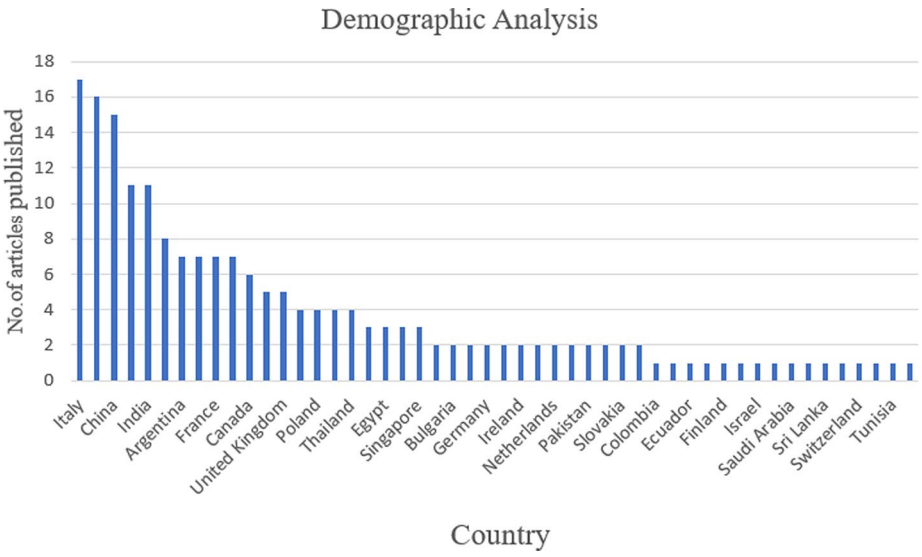


Fig. 4 Exploring global trends in *Saccharomyces cerevisiae* research: a scopus database analysis

A search technique was developed using the power of Boolean operators to thoroughly investigate the world of SC BACs in functional foods. Only relevant articles appeared in the results by methodically integrating keywords linked to yeast, its BAC, food-based applications, and possible health advantages. The search was further narrowed by using English language and research articles type filters to confidently identify the most significant research. The exact search query in the Scopus database was: TITLE-ABS-KEY ("*Saccharomyces cerevisiae*" OR "brewer's yeast" OR "baker's yeast") AND ("bioactive compounds" OR "bioactive molecules" OR "functional ingredients" OR "nutraceuticals") AND ("functional foods" OR "health benefits" OR "dietary supplements" OR "food industry" OR "food production") AND (LIMIT-TO (DOCTYPE, "ar")) AND (LIMIT-TO (LANGUAGE, "English")).

This study included specified inclusion criteria that defined the selection of studies that met certain requirements. Studies concentrating on SC BACs, including primary and secondary metabolites, were considered. In addition, studies that used in vitro, in vivo, or human clinical trials to investigate the health-promoting properties of BACs obtained from SC were included. Furthermore, research addressing the possible applications of SC BACs in the development of functional foods was included in the selection criteria, to evaluate the spectrum of health-promoting qualities and practical applications of these BAC in food production in depth.

The identified records' titles, abstracts, keywords, author names and affiliations, journal names, and year of publication were exported to an MS Excel spreadsheet. This initial approach resulted in 759 articles in the Scopus database, as illustrated in Fig. 3. After screening titles and abstracts, 544 articles were found to be inappropriate, leaving 215 for full-text evaluation. Upon additional assessment, 137 articles were eliminated, leaving 79 that satisfied the review's criteria and served as the foundation for the concluding analysis. Two independent reviewers separately examined the titles and abstracts of the records, and papers that did not meet the aims and objectives of the current review were excluded. The two reviewers then independently assessed eligibility by carefully screening the entire texts of the remaining papers. Disagreements among the reviewers were discussed and resolved by consensus at this step. If no consensus could be achieved, the opinions of a third reviewer would have been considered. All research articles about the current review's aims and objectives were included (Petticrew & Roberts, 2016).

The focus of the review was purposefully limited to original research relevant to food and health applications, omitting secondary sources such as review articles, book chapters, conference papers, short surveys, editorials, and letters. Furthermore, studies using genetically modified SC strains were removed due to potential divergence from normal strains, raising questions regarding their generalizability. To focus on understanding SC's contributions, co-fermentation studies incorporating SC were eliminated. Furthermore, applications outside of the food and health areas were avoided to maintain subject relevance. Furthermore, non-English papers were excluded to maintain data uniformity and exact interpretation across the research, which aligns with the study's search for accuracy and reliability.

2.1 Demographic analysis

The bar graph (Fig. 4) displays the distribution of articles about *Saccharomyces cerevisiae* in different countries as documented in the Scopus database. The data was obtained by

means of a thorough search that included particular keywords that indicate the purpose of the research. The keywords that were used are mentioned in Section-2 Methodology. The countries that are being considered are mentioned on the x-axis of the graph, and the number of papers published is indicated on the y-axis. Significant results show that Italy is the top contributor with 17 papers, closely followed by the United States with 16. With 15, 11, and 11 articles, respectively, China, Brazil, and India are also significantly reflected. On the other hand, it is noted that a few of countries have submitted comparatively less articles. These include Saudi Arabia, South Africa, Sri Lanka, Taiwan, Tunisia, Ukraine, Colombia, Cuba, Ecuador, Estonia, Finland, Indonesia, Israel, Saint Kitts & Nevis, and Switzerland. Even though these countries are less well-represented in the literature, there may be opportunities for more study and cooperation in the field of *Saccharomyces cerevisiae* studies.

This systematic review offers a thorough investigation of the wide range of BACs obtainable from SC. These SC-derived compounds hold immense potential to address critical societal challenges in public health and well-being. By offering a natural approach to preventing and managing chronic diseases like diabetes, obesity, and inflammation, these BACs can contribute significantly to promoting public health. Their application in functional food development can lead to the creation of more nutritious and health-promoting food products, potentially improving overall dietary patterns and reducing the risk of chronic conditions within a population. For instance, beta-glucans, a category of BACs identified in this review, have been linked to improved gut health, which can play a role in preventing chronic diseases. Furthermore, SC's versatility in fermenting a wide range of food products like yogurt, cheese, etc., contributes to sustainable food production practices, which aligns with broader societal goals of environmental responsibility. There are environmental benefits to lowering reliance on synthetic chemicals and boosting sustainable manufacturing techniques through the discovery of BACs from SC. The food and health industries stand to gain economically from this, as it has the potential to stimulate innovation and provide new job openings. A net positive effect on the economy and the environment may result from this study.

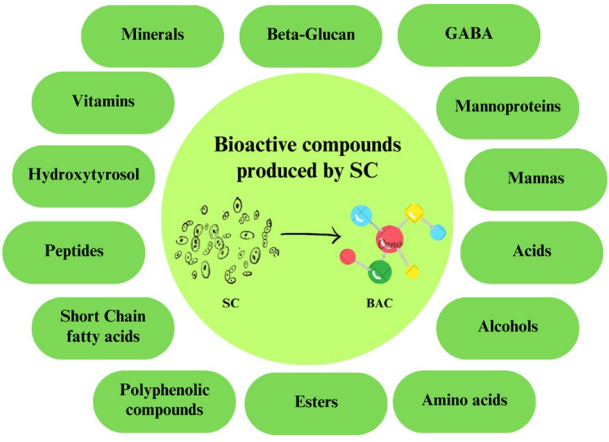


Fig. 5 Types of bioactive compounds produced by *Saccharomyces cerevisiae*

3 Results and discussions

3.1 Bioactive compounds produced by *Saccharomyces cerevisiae*

SC, commonly known as baker's yeast, is a versatile microorganism renowned for its diverse BACs, contributing to its significance in various industrial applications. The BACs produced by SC were illustrated in Fig. 5.

3.1.1 β-glucan

SC produces β-glucan, a powerful adjuvant with a wide range of biological activity and health advantages. β-glucans are glucose polymers with various anomeric configurations and glycosidic connections. These glucans are coupled to other glucose chains, mostly through the β-1,3 and β-1,6 links, and function as a barrier primarily by maintaining the cell wall due to their stiff structure of β-D-glycosidic linkages. Because they have a potent influence on the immune system, they are also employed for medicinal purposes (I Avramia & Amariei, 2021; Ionut Avramia & Amariei, 2023; Ciobanu et al., 2023). β-glucan from SC spurred the growth of macrophages and dendritic cells, yet its impact on phagocytosis and cytokine production varied across different preparations, hinting at a potential link between molecule size and diverse immune function effects (Javmen et al., 2017). Extraction methods, such as autolysis with hot water (Fu et al., 2022) and Pulsed Electric Fields (PEF) treatment, have been employed to obtain β-glucans from SC, showcasing their potential applications in various industries (Berzosa et al., 2023).

3.1.2 Gamma-aminobutyric acid (GABA)

GABA is a neurotransmitter that is essential for controlling brain activity. A nonprotein amino acid, GABA is one of the bioactive amines, mostly created by the enzyme glutamic acid decarboxylase (GAD), which catalyzes the irreversible decarboxylation of glutamic acid. The cheese fermented with SC DL6-20 exhibited lowered GABA levels (Li et al., 2021), while SC had raised GABA levels (Li et al., 2022).

The study by Yılmaz & Gökmen, 2018, (Yılmaz & Gökmen, 2018) aimed to explore SC's impact on wort fermentation, focusing on GABA and other bioactive amines. GABA levels increased in undamaged wort over 8 days and reached 534.10 mg/L in destroyed wort. Undamaged wort showed no tyramine or histamine, while ruined wort had 142 mg/L of tyramine and 130 mg/L of histamine by fermentation end. SC was identified as the GABA source, not a microbial infection. Future research should delve into protease activity and biogenic amine production in fermented foods.

3.1.3 Mannas and mannoproteins (MP)

MPs are made up of proteins that are covalently attached to sugars, primarily mannose. The strength and stiffness of the cell wall are greatly enhanced by MPs, which shield the yeast from outside factors and help it to retain its unique form. Moreover, the cell wall of yeast, which makes up 15–30% of its dry weight, may contain important substances including β-glucans and MPs. They make about 35–40% (w/w) of the dry weight of yeast cell walls.

PEF treatment of yeast biomass results in the production of MPs, contributing to the structural and functional properties of SC (Berzosa et al., 2023).

Additionally, sugarcane straw SC fermentation produces prebiotic short-chain fatty acids (SCFA) such butyrate, propionate, and acetate. Through their roles as energy pro up of a complex carbohydrate that is highly branched, with side chains of mannose that are linked by α-1,2 and α-1,3 and a main chain made of the α-1,6 backbone. Mannans have been shown to have a number of biological characteristics, including the ability to reduce pathogen adhesion, control bacterial growth, and enhance immune response, offering potential benefits for human health. Additionally, there may be an antioxidant effect due to the capacity to scavenge radicals such hydroxyl radicals and superoxide anions. Furthermore, due to their physicochemical characteristics (water solubility, viscosity, and stability), mannans exhibit a variety of techno-functional features that make them appealing for usage in food applications; these properties are primarily based on their use as an emulsion stabilizer and hardener ingredient (Faustino et al., 2022).

3.1.4 Acids and alcohols

SC plays a crucial role in the production of various organic acids, such as acetic acid, butanoic acid, hexanoic acid, and octanoic acid (Li et al., 2022). Additionally, SC contributes to the production of lactic acid, showcasing its involvement in different metabolic pathways (Mu et al., 2023).

Ethanol is the fermentation byproduct of SC that is most notable. This yeast goes through a process known as alcoholic fermentation to carry out cellular respiration under anaerobic conditions. As a result of the conversion of glucose into ethanol and carbon dioxide, adenosine triphosphate (ATP), is produced as energy. The flavors and fragrances of fermented foods like wine, beer, and bread are greatly enhanced by additional alcohols such as 1-propanol, 3-methyl-1-butanol, isoamyl alcohol, and phenethyl alcohol. The temperature at which they ferment, the type of yeast used, and the availability of nutrients all affect their production (Li et al., 2022; Mu et al., 2023).

3.1.5 Amino acids

A significant portion of the dry weight of brewing yeast residue is made up of proteins; between 35 and 60%. These proteins have a high biological value, showing that they are effective in supporting body activities, and they include all of the essential amino acids required for human nutrition. These proteins make up an important part of brewing yeast and greatly influence its residual composition.

SC, is a notable source of several amino acids. These amino acids include ornithine, glutamic acid, alanine, and glutamine; each has a unique function in the nutritional makeup of products that use brewing yeast. These amino acids play a critical role in improving the nutritional content of the finished goods that contain brewing yeast, therefore raising their total dietary value (Amorim et al., 2016; Mu et al., 2023).

3.1.6 Esters

SC is an important ingredient in fermentation, that actively participates in the synthesis of esters, including octanoic acid ethyl ester and acetic acid ethyl ester, which add to the complex flavor and aroma profiles of fermented foods. SC catalyzes esterification reactions with its enzymatic machinery, producing fruity and floral notes in drinks and fruity and solvent-like nuances in fragrances. Esters are formed in response to a range of stimuli, including pH, availability of nutrients, and conditions during fermentation. The quantity and type of esters produced can also be impacted by the genetic composition of the yeast strain. SC plays a critical role in influencing the sensory qualities of fermented items by adding a wide range of tastes and odors through its involvement in ester formation (Li et al., 2022).

3.1.7 Polyphenolic compounds, short-chain fatty acids and peptides

Sugarcane straw fermented by SC yields postbiotics that are rich in polyphenolic compounds, the main component of which is hydroxycinnamic acid. These substances add to the possible health advantages of SC-derived products, as do trace amounts of flavonoids and hydroxybenzoic acids. Owing to their antioxidant qualities, polyphenolic compounds have been connected to a number of health-promoting outcomes, such as anti-inflammatory and antibacterial actions (Oliveira et al., 2023). A phenolic molecule with known bioactivity, hydroxytyrosol (HT) has been identified in wines, although not much is known about its source. It might develop from the breakdown or alteration of other polyphenolic compounds found in wine. According to the study, SC strain QA23 is the most efficient at using artificial media and controlled fermentations with a variety of grape varietals to produce HT, a bioactive phenolic chemical. HT levels in wine varied according to grape variety and peaked on the fourth and sixth days of fermentation. This highlights how much potential SC has to produce HT during the winemaking process (Álvarez-Fernández et al., 2018) viders for intestinal epithelial cells, immune response modulators, and promoters of the formation of beneficial gut microbiota, these SCFAs are essential for gut health maintenance. The potential of SC-derived products to support digestive health and general well-being is highlighted by the presence of SCFAs formed from SC fermentation (Oliveira et al., 2023).

Furthermore, glutathione and other peptides are produced when yeast biomass is treated with a pulsed electric field (PEF). By scavenging free radicals and lowering oxidative stress, these peptides contribute to the antioxidant qualities of products derived from SC. Among the powerful antioxidants found in SC-derived products is glutathione, which is essential for cellular defense mechanisms against oxidative damage and contributes to numerous health advantages (Berzosa et al., 2023).

In summary, whereas PEF treatment of yeast biomass increases the antioxidant capabilities through the formation of peptides like glutathione, SC fermentation of sugarcane straw provides postbiotics rich in polyphenolic substances and prebiotic SCFAs. These results demonstrate the potential of products generated from SC to enhance health and well-being due to their wide range of bioactive components.

3.1.8 Vitamins and minerals

Brewer's yeast is a rich source of important vitamins, including fat-soluble vitamins A and E and seven water-soluble B-group vitamins (B1, B2, B3, B5, B6, B7, and B9). These vitamins are essential for the body's many physiological functions, such as immunological response, energy metabolism, and cellular maintenance. Brewer's yeast is a valuable dietary supplement because of the additional nutritional benefit that these vitamins provide (Mateeva et al., 2023).

Additionally, SC contains salt and potassium, two important minerals. Among other physiological activities, these minerals are essential for maintaining fluid balance, neuron function, and muscle contraction. The fact that SC contains salt and potassium emphasizes its nutritional value as a source of vital minerals (Amorim et al., 2016). Furthermore, it has been shown that ultrasonic treatment is a potential method for encouraging zinc bioaccumulation in yeast. Through the use of ultrasonic treatment, zinc bioaccumulation in yeast can be enhanced, leading to the production of zinc-enriched yeast that may find use in food and nutritional products. This creative method provides an innovative approach to treating zinc deficiency and improving the nutritional value of products made from yeast (Zahra Chitsaz Esfahani, 2023).

In a nutshell, baker's yeast, or SC, is a multipurpose microbe that generates a range of BACs. These comprise HT, squalene, polyphenolic compounds, β-glucan, GABA, mannoproteins, mannans, acids, alcohols, amino acids, esters, and peptides. The variety of BACs found in SC contributes to its function in flavor formation, fermentation, and possible health advantages. Its importance for gut health and winemaking is highlighted by its capacity to produce prebiotics and antioxidants. SC's value is further increased by its nutritional profile, which includes important vitamins and minerals. Having been considered, SC is essential in many industrial and medical applications because of its diverse range of capabilities.

3.2 Health applications of *Saccharomyces cerevisiae*

The various applications of SC in health promotion were represented in Fig. 6.

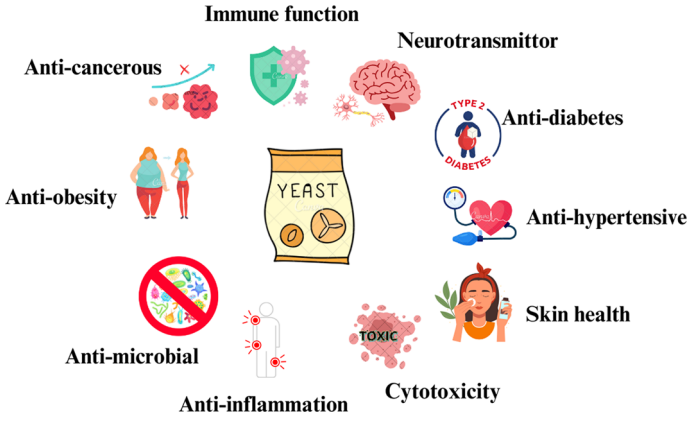


Fig. 6 Various health applications of *Saccharomyces cerevisiae*

3.2.1 Antioxidant activity

Yeast and its derivatives have been the subject of extensive research, which has demonstrated their remarkable antioxidant capabilities. Several studies have also offered comprehensive insights into the potential health advantages of these substances.

The peptide-rich extract from spent yeast showed impressive antioxidant activities making them potential allies in managing oxidative stress (Oliveira et al., 2023). According to Mirzaei et al. (2015)'s study yeast hydrolysate which is high in antioxidants and Angiotensin-converting enzyme (ACE)-inhibitory peptides looks to be a viable option for regulating blood pressure and reducing oxidative stress. Extensive research on yeast-based fermentation methods yields convincing results.

Oat bran that had been fermented by yeast had higher concentrations of DPPH (2,2-diphenyl-1-picrylhydrazyl), Radical Scavenging Activity (RSA), and ferric-reducing capacity. This increase indicates a higher level of antioxidant capability, which may have applications in the promotion of overall wellness (Mustafa et al., 2022). The unfermented decoction outperformed the fermented *Camellia japonica* petal wine by SC in terms of DPPH scavenging efficacy, demonstrating the significant antioxidant activity of the unfermented equivalent (Majumder et al., 2022).

The antioxidant potential of SC by demonstrating that the SC-fermented vine tea demonstrates strong scavenging action against various free radicals, such as DPPH, ABTS (2,2-azino-bis-3-ethylbenzothiazoline-6-sulphonic acid), hydroxyl, and superoxide anion radicals. Yeast-fermented products are useful in the fight against oxidative stress because of their broad antioxidant activity (Xu et al., 2022). Beyond conventional uses, peptide extracts from β-glucan waste streams and mannan extraction techniques from discarded yeast has been investigated (Oliveira et al., 2022). The ensuing extracts showed effective scavenging of free radicals, including DPPH and ABTS, indicating a possible path for waste valorization and antioxidative uses.

Research on the antioxidant characteristics of SC Y3 exopolysaccharide (EPS) by showed strong thermal stability and strong antioxidant activities (L. Liu et al., 2022). These discoveries demonstrate the adaptability of chemicals generated from yeast and open up opportunities for integrating EPS into different food products and fermentation processes. Fermentation of spelled seeds that had germinated using SC produced the largest amounts of extractable individual phenolics and in vitro antioxidant activity (Mencin et al., 2022). This highlights how yeast can improve the nutritional profile and antioxidant content of particular foods. According to the findings, β -glucan isolated from SC possesses antioxidant activity and may be a major factor in reducing the harmful effects of lead (Tatli Seven et al., 2021).

Significant antioxidant activity against DPPH and ABTS was demonstrated by the SC extract, which also showed a noteworthy Ferric reducing ability of plasma (FRAP) value expressed in ascorbic acid equivalents. Because they function as organic antioxidants, SC's secondary metabolites could find use in medical and commercial applications (Makky et al., 2021).

The DPPH radical scavenging activity and ferric reducing power of a 2–10 kDa peptide fraction produced from SC metabolism were examined, providing insight into the precise chemical elements accountable for antioxidant actions (Branco et al., 2023). In their investigation of postbiotics obtained from SC fermentation of sugarcane straw, these microorgan-

isms have antioxidative and free radical-neutralizing properties (Oliveira et al., 2023). This discovery raises the possibility of using these postbiotics to reduce oxidative damage and promote health.

Molecules with the highest antioxidant activity were generated at temperatures below 60 °C, demonstrating the critical impact that temperature plays in antioxidant activity (Ciobanu et al., 2023). This temperature-dependent feature adds another level of complexity to the optimization of antioxidant synthesis obtained from yeast. Finally, compared to non-fermented cinnamon, the antioxidant activity of SC fermented cinnamon extract was found to be much higher (Darwesh et al., 2023). The evaluation by ABTS, DPPH, and H_2O_2 radical scavenging assays stresses the potential of yeast fermentation in increasing the antioxidant activities of natural extracts.

After simulated digestion, SC autolysates showed increased antioxidant and ACE-inhibitory activity, proved safe for intestinal cells, provided protection against oxidative stress, exhibited high gut absorption with efficient permeability across cell models, and demonstrated absorption of beneficial compounds like antioxidants and ACE-inhibitors across the intestinal barrier (Vieira et al., 2016).

In conclusion, a large amount of evidence points to yeast and its derivatives' strong antioxidant potential. These discoveries pave the way for the creation of functional foods and BACs with potential health benefits, in addition to furthering our understanding of yeast-mediated processes.

3.2.2 Anti-inflammatory activity

Notable results were obtained from the study on the anti-inflammatory properties of SC strains, specifically ITEM 14,093 and ITEM 14,077, which are utilized in the vinification of Primitivo and Negroamaro grapes. When compared to wines made with other yeast types, Wines fermented with these particular SC strains showed reduced vascular inflammation in a model, suggesting possible health advantages (Grieco et al., 2019). This observation suggests that the inflammatory characteristics of the final wine can be influenced by the selection of yeast strains during the fermentation process.

The anti-inflammatory properties of SC-fermented vine tea were proven in an inflammation model using zebrafish in a different setting. This specific fermentation process had a beneficial effect on the regulation of inflammation because it decreased the recruitment of inflammatory cells (Xu et al., 2022). Branco et al. (2023) offered additional insights into the molecular mechanisms underlying SC-mediated anti-inflammatory actions (Branco et al., 2023). They found that (Tumour Necrosis Factor) TNF-α gene expression in colon cells was considerably decreased by a 2–10 kDa peptide fraction produced from SC metabolism. With a significant 50% drop in lipopolysaccharide-stimulated cells and a notable 29.7% decrease in non-stimulated cells, the reduction was especially striking. These results demonstrate the ability of peptides produced from SCs to alter inflammatory responses at the genetic level.

The anti-inflammatory qualities of postbiotics produced during SC fermentation of sugarcane straw were also studied. These postbiotics have a strong anti-inflammatory effect because they reduce the pro-inflammatory mediators TNF-α and IL-8 in Caco-2 cells. This implies that SC-derived postbiotics may be used to treat illnesses associated with inflammation (Oliveira et al., 2023). Furthermore, Darwesh et al. (2023) investigated the anti-inflam-

matory properties of SC-fermented cinnamon extract. According to the study, cinnamon's natural anti-inflammatory qualities were strengthened by this extract, which resulted in a greater ability to combat inflammatory indicators. This suggests that the BACs in cinnamon that cause its anti-inflammatory properties may be enhanced by the fermentation process (Darwesh et al., 2023).

Through a variety of processes, the β-glucan isolated from baker's yeast showed a considerable reduction in inflammation in colitis-affected rats. First of all, it suppresses mediators of inflammation and oxidative stress. Second, it improved the expression of proteins known as tight junctions, which support the integrity of the intestinal barrier. Furthermore, it modulated the production of SCFAs by gut bacteria. According to this study, β-glucan from baker's yeast is a powerful and promising anti-inflammatory agent. Its unique composition and potency in treating colitis point to the possibility of creating novel treatment modalities for inflammatory bowel conditions (Qiao et al., 2022).

As a whole, these investigations offer strong proof of SC and its derivatives' ability to reduce inflammation. The results point to a wide range of uses for yeast-based products in reducing inflammation and enhancing health, whether through the use of particular yeast strains in the fermentation of wine, SC-fermented grape tea, peptides produced from SC, postbiotics, or fermented cinnamon extract.

3.2.3 Antimicrobial activity

Promising results about the application of particular compounds obtained from yeast are found in the study of antibacterial activity.

Now for the antimicrobial qualities: *Salmonella sp*., *Escherichia coli*, *Candida albicans*, and *Listeria monocytogenes* were all successfully inhibited by a 2–10 kDa peptide fraction generated from SC metabolism. However, Branco et al. (2023) showed that it did not show an antimicrobial effect against *Candida krusei* (Branco et al., 2023). This suggests possible uses in focusing on particular diseases by demonstrating a selective antibacterial action. Darwesh et al. (2023) investigated the antibacterial activity of SC fermented cinnamon extract in a distinct investigation (Darwesh et al., 2023). *Salmonella typhi*, *Candida albicans*, *Staphylococcus aureus*, *Escherichia coli*, *Listeria monocytogenes*, and other foodborne and pathogenic bacteria were all susceptible to the antibacterial activity of this extract. This broad-spectrum antibacterial action suggests that it may be useful in the fight against a range of microbiological problems.

Significant antibacterial activities were demonstrated by the SC extract against *Staphylococcus aureus* and *Staphylococcus epidermidis* at lower doses, but greater concentrations were needed to be effective against *Cutibacterium acnes*. The extract exhibited remarkable sensitivity towards *Staphylococcus aureus*. Because the extract contains a variety of phytochemical ingredients, these metabolites showed high antibacterial action against the tested pathogens (Makky et al., 2021).

In conclusion, there are a variety of uses for compounds obtained from yeast that have antibacterial action. Specific peptide fractions from SC metabolism and fermented cinnamon extract show promise antibacterial activity against a spectrum of pathogens. These results further the investigation of yeast-based remedies for microbial control and well-being.

3.2.4 Antidiabetic activity

A promising natural cure for type 2 diabetes mellitus may be black rice yeast extract (BRYE), as studies showing beneficial effects on blood glucose levels in diabetes-induced animals have led to this conclusion. BRYE contains BACs such as anthocyanins, flavonoids, and chromium that are likely responsible for the observed effects. This implies that BRYE's ability to regulate blood glucose may help manage type 2 diabetes (Agustini et al., 2021).

A 2–10 kDa peptide fraction produced from this method showed antidiabetic efficacy in the setting of SC metabolism. A decrease in α-amylase and α-glucosidase activity was found by Branco et al. (2023), suggesting possible advantages for blood glucose regulation and carbohydrate metabolism. This discovery emphasizes the bioactive capacity of certain peptides generated during the metabolism of SC to contribute to antidiabetic effects (Branco et al., 2023). Additionally, as shown by Dumitrașcu et al. (2023), SC had good anti-diabetic efficacy in the fermented product when compared to an unfermented decoction. This shows that the fermentation process, enhanced by SC, boosts the putative antidiabetic effects of the beverage obtained from *Camellia japonica* petals (Dumitrașcu et al., 2023).

In conclusion, research on SC metabolism and BRYE suggests that these compounds may have anti-diabetic properties. The investigation of natural remedies for type 2 diabetes mellitus is aided by the beneficial effects of fermented items on blood glucose levels, the decrease in important enzyme activity, and the increased anti-diabetic action.

3.2.5 Cytotoxicity

Cytotoxicity refers to the ability of a substance or process to damage or kill cells. Essentially, anything that is toxic to cells exhibits cytotoxicity. In both colorectal cancer and normal colon epithelial cells, the 2–10 kDa peptide fraction derived from SC metabolism shows minimal cytotoxicity, even at concentrations as high as 0.3 mg/mL. According to Branco et al., 2023, these cells appear to tolerate the peptide fraction well, suggesting that there are no deleterious impacts on cellular survival. Positively, the lack of cytotoxicity may allow for additional research into this peptide fraction for possible therapeutic uses without harming healthy colon epithelial cells or colorectal cancer cells.

3.2.6 Anti-cancerous activity

The ability of a substance or drug to slow down or prevent the onset or spread of cancer is known as anticancerous activity. In one study, mouse melanoma B16-F10 cells' tumor cell activity and tyrosinase activity (melanin production) were both inhibited by SC-fermented grape tea. This implies anti-melanoma activity, indicating a potential function in attacking melanoma cells. Xu et al. (2022) presented similar data, underscoring the potential of SC-fermented vine tea as a candidate for interventions linked to melanoma. In a similar vein, Huh7 cancer cells responded favorably to SCFC. This implies possible uses in the treatment or prevention of cancer (Xu et al., 2022). The Darwesh et al. (2023) study demonstrates the beneficial effects of SC fermented cinnamon extract on particular cancer cells, suggesting that it may play a part in resolving cancer-related issues (Darwesh et al., 2023).

To summarize, the results imply that SC and its fermented derivatives might have anticancer qualities, which makes them intriguing subjects for additional investigation in cancer studies and medicinal uses.

3.2.7 Neurotransmitter

SC is known to produce GABA in cheese, which can raise GABA levels. GABA is a neurotransmitter that is essential for controlling brain activity. There may be health benefits to this rise in GABA levels brought on by SC activity in cheese, especially in terms of lowering anxiety and enhancing mood. GABA level modulation is linked to a soothing effect on the neurological system, which suggests that it may help to promote mental health (Li et al., 2022). This demonstrates how SC-produced GABA in cheese may affect neurological and psychological functions, providing a possible line of inquiry into the relationship between nutrition, neurotransmitters, and mental health.

3.2.8 Immune function

β-glucan, a yeast component, has been known to have immunomodulatory effects. β-glucan can stimulate specific immune cells, which could enhance the immune system's ability to fight against infections and illnesses (Fu et al., 2022). This suggests that β-glucan plays a part in strengthening the body's defense mechanisms against different kinds of infections. The work by Higuchi et al. (2023) looks into SC extracellular vesicles (SC-EVs) as a possible vaccine material (Higuchi et al., 2023). The study highlights several features of SC-EVs, such as their size, surface charge, and contents including HSP70 and β-D-glucan. It was shown that SC-EVs stimulated the production of pro-inflammatory cytokines in cells, increased the maturation of immune cells by upregulating certain markers, and stimulated the immune system by endocytosing toll-like receptor 2. These results point to the possible use of SC-EVs in inducing immunological responses, which raises the possibility that they could be useful in the creation of vaccines.

To sum up, studies conducted on baker's yeast autolysate, β-glucan, and SC-EV collectively indicate that components generated from yeast may have the ability to improve immunological function. These results advance our knowledge of yeast's immunomodulatory capabilities and possible uses in enhancing immunological function.

3.2.9 Antihypertensive

The peptide-rich extract from spent yeast showed impressive antihypertensive making their potential allies in managing blood pressure (Oliveira et al., 2022). Amorim et al.'s (2019) study emphasizes the antioxidant and antihypertensive qualities of a wasted brewer's yeast fraction. This fraction shows promise for the prevention and treatment of hypertension because it is effectively absorbed and lowers blood pressure in animals. According to the study, the spent brewer's yeast fraction might help control hypertension and enhance cardiovascular health in general (Amorim et al., 2019).

As a natural antihypertensive therapy, carboxymethyl-glucan, a derivative of β-D-glucan isolated from SC, exhibits the potential to lower blood pressure, enhance baroreflex sensitivity, and reduce sympathetic tone (Bezerra et al., 2021). Furthermore, Oliveira et al.

(2022) concentrated on peptide extracts that were derived from the byproducts of the extraction operations of mannan and β-glucan from spent yeast. The ACE activity was significantly suppressed by these peptide extracts. The inhibition of ACE activity is significant since ACE is essential for controlling blood pressure. The results point to a potential use of the peptide extracts in the treatment of hypertension by suggesting that they may help regulate blood pressure (Oliveira et al., 2022).

In conclusion, peptide extracts from waste streams and discarded brewer's yeast fraction have both been studied and shown promise as antihypertensive drugs. These results further the investigation of the potential roles that components derived from yeast may have in controlling blood pressure and maintaining cardiovascular health.

3.2.10 Anti-obesity

Numerous research shed light on the possible ability of certain yeast-derived components to reduce cholesterol and help people lose weight:

HMG-CoA (Hydroxymethylglutaryl-CoA) reductase has been discovered to be strongly inhibited by peptide extracts obtained from the waste streams of β-glucan and mannan extraction methods from discarded yeast. Given that HMG-CoA reductase is a crucial enzyme in the manufacture of cholesterol, this suggests that the substance may have cholesterol-lowering qualities (Oliveira et al., 2022). The peptide extracts may have a function in controlling cholesterol levels, as indicated by the suppression of this particular enzyme.

LipiGo®, a polysaccharide-rich supplement made from SC, was studied for its impact on weight loss in overweight and obese persons over 12 weeks. According to Santas et al. (2017), those taking LipiGo®'s BGCC (beta-glucan-chitin-chitosan) component had a marginally smaller waist circumference and lower body weight than the placebo group. This implies that consistent BGCC dosage may help reduce weight without causing noticeable side effects, suggesting a possible function in weight management. The impact of fermented citrus peel on obesity in rats given a high-fat diet was studied. Fermented citrus peel promoted visceral fat breakdown, reduced the production of liver fat, and offered defense against oxidative stress. These results emphasize the potential function of fermented citrus peel in weight control and liver health by suggesting that it may be able to mitigate obesity-related variables (Huang et al., 2022).

In summary, the studies collectively demonstrate the potential of yeast-derived peptide extracts, polysaccharide-rich supplements like LipiGo®, and fermented orange peel in addressing cholesterol levels, weight management, and obesity-related issues. These results further the investigation of components produced from yeast and their possible uses in enhancing cardiovascular health and general well-being.

3.2.11 Skin health

Cellulase saccharification converted straw into fermentable sugars, which resulted in a postbiotic extract via SC fermentation. This extract contained beneficial substances such as sorbitol for hydration, acetate, and citrate for anti-inflammatory properties, azelaic and sebacic acids for antibacterial and anti-aging properties, and different polyphenols for antioxidants and photoprotection. Its skincare promise rests in its ability to block skin-degrading

enzymes, improve skin barrier restoration, and restrict the growth of dangerous microbes (Duarte et al., 2023).

3.2.12 Liver protection and gut health

Brewer's yeast extract (BRYE), has shown promise as a therapeutic agent to protect liver health from the damaging effects of diabetes. Research has indicated that it may play a part in improving liver regeneration and boosting antioxidant enzyme activity in the liver by protecting liver cells in diabetic mice. The results highlight the potential of BRYE as a natural remedy to mitigate diabetes-related liver problems and call for more research into the mechanisms beneath its action (Agustini et al., 2021).

β-glucan, found in brewer's yeast extract, can withstand digestion in the small intestine and make its way to the colon. As a prebiotic that feeds gut bacteria and promotes a healthy intestinal environment, this property is beneficial to digestion and gut health. It also has therapeutic potential in cardiovascular health and lipid metabolism because it binds to bile acids and prevents their reabsorption, increasing excretion and possibly decreasing blood cholesterol levels (Fu et al., 2022).

In conclusion, SC and its derivatives have a wide range of health advantages and present possibilities for the development of functional foods and BACs with possible medical uses. The diverse range of health-promoting attributes exhibited by SC highlights its importance across various industries and research fields.

3.3 Applications of *Saccharomyces cerevisiae* in the food industry

The various food applications of bioactive compounds produced by SC were discussed in the Fig. 7.

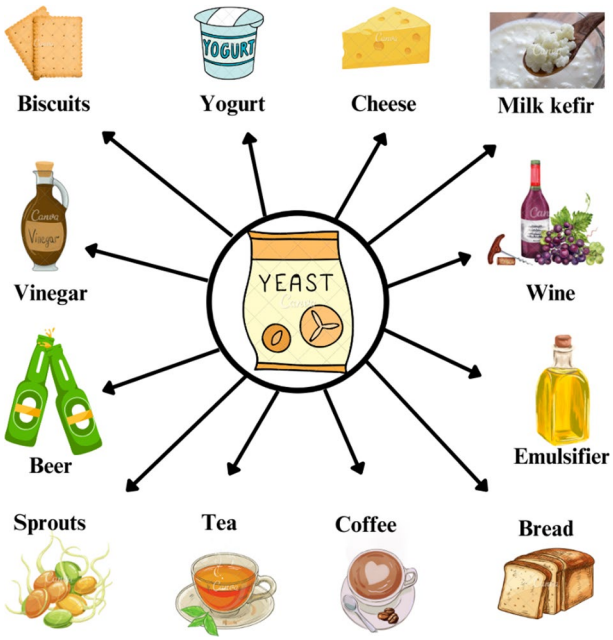


Fig. 7 Applications of *Saccharomyces cerevisiae* in the food industry

3.3.1 Cheese production

SC can be employed as a starter culture or as an additional culture in cheese production. It aids in the fermentation process, which improves the flavor and texture of the cheese. Furthermore, SC can create volatile aromatic chemicals that add to the cheese's overall odor character (Li et al., 2022). SC DL6–20 fermented cheese showed remarkable aroma production capabilities, outperforming other explored yeast strains. Its GABA concentration dropped throughout fermentation, but its protein and amino acid balance remained ideal (Li et al., 2021).

3.3.2 Tea and coffee

BACs such as 5-(hydroxymethyl)-2-furaldehyde, furfural, and alpha-methylene-gamma-butyrolactone were produced through the fermentation of tea petal decoction with the help of SC (Majumder et al., 2022). The relevance of SC-mediated fermentation in the production of BACs from tea petals is highlighted by the identification of these compounds as possible antioxidant molecules. In the same way, Kim et al. (2022) investigated the effects of SC fermentation on green coffee beans and discovered a unique profile of metabolites that included amines, sugars, acids, alcohols, and amino acids. This study highlights the flexibility of SC fermentation in modifying coffee flavor characteristics through the synthesis of certain metabolites (Kim et al., 2022).

The results of these experiments provide important new information about how SC might be used in the fermentation process to improve the bioactive and flavor-related qualities of tea and coffee.

3.3.3 Beverages

Avîrvarei et al. (2023) have suggested that the revival of mead, a honey-based beverage fermented with SC, has shown good results in conserving rosehip flavonoids like catechin and phenolic acids like protocatechuic acid. These substances, which have anti-inflammatory and antioxidant qualities, raise the possibility of health advantages from mead consumption (Avîrvarei et al., 2023). He et al. (2023) examine how the fermentation of SC affects the phenolic content and sensory quality of pear beverages, emphasizing the important role that SC plays in these areas. This work advances our knowledge of how SC influences the sensory and chemical characteristics of fermented pear beverages (He et al., 2023).

Mu et al. (2023) report that using SC BR14 during the manufacturing of Huangjiu, a Chinese alcoholic beverage, results in significant extra health advantages. Enhanced immune response capacity, decreased inflammation, and elevated antiradical activity are a few of them (Mu et al., 2023). The results point to the possible application of SC BR14 as a functional food additive to improve Huangjiu's nutritional profile and hence support health and wellbeing.

Overall, this research highlights how SC can be used to modify the taste, composition, and health benefits of a wide range of fermented drinks, including mead, huangjiu, and pear beverages.

3.3.4 Wine

Numerous studies demonstrate the importance of SC in a variety of fermentation processes, especially those related to winemaking and beverage manufacturing. Liu et al. (2022) highlight the critical significance that SC plays in cherry winemaking, primarily attributing its role to the synthesis of volatile compounds that are necessary to achieve the desired flavor character (Liu et al., 2022). The potential health benefits of SC-fermented vine tea are revealed, who show that the resulting probiotic broth has anti-inflammatory, antioxidant, and anti-melanoma properties (Xu et al., 2022).

In their investigation of the fermentation of Jimbee and Okashi wines using SC, Salas-Millán et al. (2022) observed changes in antioxidant capacity while preserving high amounts of phenolic compounds, particularly in melon wines, which may have health benefits (Salas-Millán et al., 2022). The effects of SC strains on wine production are explored in Lachowicz et al. (2017) and Li et al. (2017), wherein Lachowicz et al. emphasize the superior antioxidant activity of SC SIHA WHITEAROME in chokeberry wine, while Li et al. highlight the impact of yeast selection on alcohol, acidity, and aroma in kiwifruit wine (Lachowicz et al., 2017); (Li et al., 2017).

Using SC to ferment Dangshan pear resulted in a dry wine with 14.1% alcohol and 3.13 g/L sugar in only 15 days, boosting overall acidity mostly with malic acid, confirming SC's suitability for Dangshan pear wine and potentially expanding the usage of this particular pear in winemaking (Yang et al., 2019).

The BM45® strain produced the greatest amount of beneficial compounds during alcoholic fermentation, including reduced glutathione (Guerrini et al., 2018). The synthetic wines from different SC strains display antioxidant and anti-inflammatory characteristics, equivalent to ascorbic acid. Furthermore, the brewing of beer from buckwheat and found that hydrolyzing buckwheat phytates can promote SC metabolism during wort fermentation (Duliński et al., 2020). The study also finds that the buckwheat wort has higher amounts of Zn^{2+} ions and myo-inositol. Response surface technology was used to ferment jamun fruit with SC, resulting in a high-ethanol content wine that was stable, nutritious, and well-received (Singh & Kocher, 2020).

The best outcomes were obtained by using SC EC-1118 yeast that had 50% seed content, 20% initial soluble solids, and a fermentation temperature of 30 °C. The initial sugar concentration and fermentation temperature had no influence, however the antioxidant activity of the yeast strains varied. Phenethyl alcohol, 2,3-butylene glycol, ethyl hydrogen succinate, 5-hydroxymethyl-2-furaldehyde, and 4-hydroxyphenyl alcohol were among the dominant compounds that substantially affected the total antioxidant activity (Tandee et al., 2021).

Lastly, Capece et al. (2020) suggest reducing the requirement for sulfur dioxide (SO_2) addition in winemaking by using specific SC starting cultures. When taken as a whole, these studies offer insightful information about the many uses and effects of SC in fermentation processes, highlighting how it influences the taste, bioactive composition, and health-related characteristics of different fermented products (Capece et al., 2020).

SC is a crucial component in fermentation processes, especially winemaking, where it is shown to have a role in the synthesis of flavor and contribute to the production of antioxidant-rich drinks such as SC-fermented vine tea. Research highlights the adaptability of SC in fruit fermentation, indicating that it may improve the BACs and health-related attributes of a range of fermented products.

3.3.5 Beer

Numerous research works demonstrate the various uses of SC in the brewing sector, especially in the manufacturing of beer and associated beverages. Dziedziński et al. (2023) investigate whether using pine shoots and particular SC strains can result in low-alcohol beers that may have functional advantages. Pine shoots boost the beer's antioxidant content without interfering with the brewing process, and various yeast strains contribute to a range of flavor and scent characteristics that may help cover up unwanted aromas from non-traditional yeasts (Dziedziński et al., 2023).

Díaz-Muñoz et al. (2023) show that adding a SC strain to the fermentation process increases the production of flavor during the fermentation and drying stages of the cocoa fermentation process. As a result, cocoa beverages and chocolates have smell profiles that are deeper and more consistent. Based on the sensory analysis, it can be concluded that the higher fermentation level in SC-produced cocoa liquors and chocolate results in more tart flavors than in spontaneous fermentation (Díaz-Muñoz et al., 2023).

The impact of four distinct yeast strains on the chemical composition and antioxidant capacity of American Pale Ale craft beer was examined (Viana et al., 2021). Lower antioxidant capacity but higher lactic acid and lower acetic and succinic acid levels were produced by US-05 yeast, which may have contributed to the desired flavor profile. Beer made with M15 yeast has a higher concentration of malic and formic acid but a lower alcohol and antioxidant capacity. Higher glycerol-content beers were produced by S-04 yeast, and higher alcohol-content beers were produced by BRY-97 yeast strains. These results demonstrate how important it is to select the right yeast strain for the functional and sensory qualities of these craft beers.

Three SC strains (CHE-3, P4, and TA4-10) are studied by (Siesto et al., 2023) Siesto et al. (2023) about beer fermentation, specifically in malt extracts that have adjuncts of grape must. These strains produce CO_2 more efficiently than a commercial strain, and the inclusion of grape must and yeast strain has a major impact on the experimental beers' volatile components and analytical qualities. The most distinctive odor characteristics are obtained by adding 15% grape must. Sorghum beer derived from SC has strong antioxidant activity, pointing to possible health advantages of consuming it (Coulibaly et al., 2020).

Francesca et al. (2023) improve the sensory qualities of loquat beer by commencing with SC MN113 extracted from manna (Francesca et al., 2023). Due to the strain's improved scent awareness, balanced flavor profile, and higher residual sugar content, these beers could be used to produce sour and fruit beers. The study explores how different yeast strains, β-cyclodextrin (BCD) addition, and storage time impact red apple cider quality. Specifically, using the SIHAFERM Finesse Red strain with BCD led to improved characteristics and potential antioxidants in the cider (Lachowicz et al., 2019).

Mu et al. (2023) stress the importance of SC BR14 as an extra starter in the manufacture of Huangjiu, enhancing its nutritional value, scent profile, fermentation efficiency, and health benefits (Mu et al., 2023). This strain has the potential to produce novel functional foods because of its capacity to decrease ethyl carbamate precursors and elicit an immune response.

All of this research highlights how SC can influence the properties and traits of a wide range of fermented drinks, from beer to cocoa liquors and Huangjiu.

3.3.6 Biscuits

(Silva et al., 2018) de Oliveira Silva et al.'s (2018) investigation concentrated on the effects of dry heating and SC fermentation on the composition of soybean meal. Trypsin inhibitors, lipids, and carbs were all considerably decreased throughout the fermentation process, which also boosted the amount of fiber by 50% and produced 7.8 times more isoflavone aglycones. After fermentation, there was a notable 206% increase in antioxidant activity. Although they received mixed sensory rankings, biscuits produced from aglycone-rich soybean meal outperformed wheat biscuits in terms of functioning and nutrition. According to the study, fermentation improves the nutritional value and functionality of soybean meal, though there may occasionally be problems with taste.

In a similar vein, Barreto et al. (2022) investigated the production of biscuits using fermented soybean flour and saw improvements in mineral content (excluding iron), dietary fiber, protein, and ash (Barreto et al., 2022). Furthermore, glycosylated isoflavones were transformed into aglycones, and oligosaccharides were eliminated. However, the odd aromas that the baker's yeast created during fermentation may have contributed to the biscuits' difficulty in being accepted by the senses.

In a different context, Ali et al. (2023) showed how to employ fermented and gelatinized Urad bean flour (FGUBF) from SC MK157 as a healthier fat substitute in biscuits. Saturated fat levels were reduced by up to 30% as a result of this method (Ali et al., 2023). The biscuits' levels of protein, fiber, phenols, flavonoids, and antioxidants were all raised by the combination of fermentation and gelatinization. By lowering antinutrients, fermentation also increases the digestion of proteins. The size, texture, and flavor of biscuits with 20% FGUBF were similar to those of the control biscuits. This study offers a workable plan for using fermented bean flour in biscuit recipes as a healthier substitute.

3.3.7 Vinegar

In a study by Chantarot et al. 2022, investigated the use of rice pasta by-products to produce Monascus vinegar using multiple yeast strains, including SC TISTR 5169, TISTR 5196, and TISTR 5197. Because of SC TISTR 5169's superior alcohol synthesis, the vinegar has a higher concentration of xanthine oxidase inhibitors and antioxidants (Chantarot S, 2022). Beneficial elements like monacolin K, monascus pigments, and total phenolic compounds were present in the resulting monascus vinegar. Crucially, it was discovered that the vinegar lacked mycotoxins, proving its safety for ingestion by humans. This study shows how yeast strains, especially SC, can be used to produce high-quality vinegar that contains components that are good for you.

Comparing the "Khalas" date vinegar to other commercial varieties and other date vinegar, Hamden et al. (2022) found that it had higher phenolic and carotenoid concentrations. This vinegar's higher antioxidant content raises the possibility of health benefits, which makes it a desirable ingredient to use in food and nutraceutical products. The importance of date vinegar as a source of BACs that may support general health and illness prevention is emphasized by the study (Hamden et al., 2022).

3.3.8 Fermented sprouts

Several studies have shown that SC can be used to enhance the health-promoting qualities of food made from plants through the elicitation and fermentation of sprouts.

In their investigation, Chen et al. (2020) found that fermented buckwheat sprouts (BS) had much higher DPPH and OH scavenging activities than unfermented BS (Chen et al., 2020). Fermented bovine serum reduced blood lipid markers and restored liver antioxidant levels in hyperlipidemic mice. Buckwheat sprouts' antioxidant and hypolipidemic properties were boosted by the SC-assisted fermentation process, suggesting that SC may have potential health advantages. Regular buckwheat sprouts and seeds were contrasted with those fermented with SC (Molska et al., 2022). The fermented buckwheat sprouts showed increased antioxidant capacity, a stronger anti-inflammatory effect, and a considerable increase in total phenolic components. These results imply that SC fermentation improves the buckwheat sprouts' nutritional and functional qualities, possibly lowering chronic inflammation linked to several illnesses.

In summary, the research highlights the beneficial effects of fermentation and elicitation caused by SC on the health-promoting characteristics of sprouts, such as higher phenolic synthesis, better antioxidant activity, and increased bioavailability of advantageous phytochemicals.

3.3.9 Emulsifier

The SC URM 6670 biosurfactant demonstrated strong emulsifying activity (>50%) with diverse vegetable oils, indicating its potential as a natural emulsifier in food compositions. Its versatility is enhanced by its stability across pH and temperature ranges. It improved rheological properties, worked as a natural thickening, and improved stability, texture, and overall quality when coupled with commercial emulsifiers in salad dressings (B. G. Ribeiro, Campos Guerra, & Sarubbo, 2022).

3.3.10 Yogurt

Research on the use of SC and yeast beta-glucan from brewer's yeast in yogurt production has shed light on possible effects on yogurt quality and consumer acceptance.

Raikos et al. (2018) improved textural parameters and shortened the fermentation period in yogurt production by using powdered β-glucan derived from brewer's yeast (Yestimun). Despite certain physicochemical variations, such as color, the total Likert values suggested commercialization potential (Raikos et al., 2018). According to the study, adding brewer's yeast beta-glucan to yogurt may be a workable way to improve specific textural aspects without lowering overall customer acceptability.

The addition of SC yeast β-glucan to skim milk yogurt production was studied (Santos et al., 2019). Yogurt stiffness and compactness rose with the addition of β-glucan, although syneresis also increased. Despite having a full-fat yogurt-like appearance, the yogurt's sensory qualities suggested possible commercial viability issues. This work highlights how crucial it is to take into account both the sensory and physical elements when adding particular beta-glucans to yogurt recipes.

Overall, these investigations show that adding beta-glucans produced from yeast can improve yogurt's structure, texture, and possibly even health properties. To ensure customer approval, however, meticulous evaluation of sensory qualities and commercial feasibility is essential.

3.3.11 Milk kefir

This study tells that milk kefir prepared using SC KU200284 a potential probiotic strain isolated from *Cucumber jangajji*, can be used as a starter culture for milk kefir production due to its physicochemical properties, including pH, titratable acidity, viscosity, Brix level, and alcohol content, compared to kefir prepared using only kefir grain and β-glucan production from this strain make it a suitable candidate for use as a starter culture in functional dairy products (Hong et al., 2019).

3.3.12 Grain-based products

Numerous research has investigated the application of yeast fermentation in a range of grain products, including wheat bran, brown rice flour (BRF), and wheat-based bread. The results have shown that this process has a good impact on the nutritional value, sensory qualities, and antioxidant characteristics of these products.

Potato peel (PP) increased the enzymatic activity of yeast in bread-making. The optimum SC growth occurred when the medium contained 2% PP. 4% PP significantly boosted cellulase and invertase activity, while 2% increased amylase activity. Overall, 4% PP is recommended to improve enzymatic activity and bread quality (Najmalddin et al., 2023).

Mustafa et al. (2022) found that the fermentation of oat bran by yeast significantly improved the nutritional composition and functional qualities of the grain. The amount of protein, crude fat, and total dietary fiber—which includes both soluble and insoluble components was increased during the fermentation process. This change gave oat bran enhanced antioxidant qualities in addition to having a good effect on its physicochemical and structural characteristics (Mustafa et al., 2022). According to the study, oat bran can be fermented by yeast, which increases its nutritional value and versatility and opens up new culinary and health benefits possibilities.

Protein, ash, fiber, and other minerals significantly improved when BRF was fermented solid-state using different yeast brands. The highest quantities of protein, ash, zinc, and calcium were produced by eagle yeast in particular, which also produced more antioxidants and phenolic content. Significantly, the amount of phytic acid was reduced, particularly in BRF that was fermented with Eagle yeast (Ilowefah et al., 2017). This study emphasizes how brown rice flour's nutritional composition is affected by yeast fermentation.

The polyphenol content of wheat bran—including soluble, binding, and total polyphenols—was considerably elevated by Baker's yeast fermentation. When compared to control samples, the amount of flavonoids increased and anti-nutritional components like tannins decreased. This led to a twofold increase in in vitro antioxidant capacity and a 56% increase in free radical scavenging. This suggests that the antioxidant and phytonutrient levels of wheat bran were positively influenced by Baker's yeast fermentation (Zhao et al., 2021).

The fermentation of wheat bran with SC was studied by Rezaei et al. (2019), who found improvements in soluble dietary fiber, protein, and ash. The reduction of phytic acid was

seen, particularly in certain particle sizes, with the greatest gains in soluble dietary fiber and the least amount of phytic acid. The results indicate that using fermented wheat bran in high-fiber bread is a potential application. Consumer acceptability of Tafton bread including both fermented and non-fermented wheat bran was equivalent to bread without bran (Rezaei et al., 2019).

To improve the functional qualities of the resultant doughs, Palla et al., 2021 looked into the use of particular yeast strains during the fermentation process of wholegrain flours. Researchers discovered that these yeast strains produced advantageous compounds such as propionic acid and linoleic acid and showed anti-inflammatory properties (Palla et al., 2021). They also demonstrated a notable resistance to simulated digestive fluids, indicating possible probiotic activity. The study's overall findings demonstrate the potential of these unique yeast strains as useful starters for creating novel, health-promoting fermented meals.

Collectively, these studies highlight the potential advantages of yeast fermentation in enhancing the nutritional makeup, texture, and antioxidant characteristics of different grain-based products. This holds promise for the creation of more enticing and healthful food options.

3.3.13 Other fermented products

Fruit pomace protein changed in texture and viscosity when yeast protein extract derived from SC cell walls was added. Heat processing, however, brought these qualities back, indicating a reversible effect. Crucially, Fernandes et al. (2022) work shows that fruit pomace protein can be improved by adding yeast protein extract without impairing its functions. Moreover, by binding beneficial substances like phenolics, the addition of dietary fibers, made possible by yeast protein extract, can offer further health advantages (Fernandes et al., 2022).

The study by Lee et al., 2019 investigated three SC strains isolated from *Cucumber jangajji* for probiotic properties. SC KU200284 and KU200280 demonstrated high levels of glucan and L-ornithine, respectively (Lee et al., 2019). All three strains exhibited the ability to protect DNA from oxidative stress damage. The strains also demonstrated stability and safety in gastrointestinal conditions and other environments. Overall, these findings suggest the potential use of these SC strains as probiotics and as starter cultures for functional fermented foods.

All four commercial yeasts produced a significant amount of ethanol and glycerol by efficiently using sugar. The strains of yeast T-58 and US-05 were notable for producing more lactic acid than other strains. The lack of noticeable variations in the amounts of phenolic compounds or antioxidant activity among the yeast strains is noteworthy. Hesperidin was the main phenolic component that was found. During the fermenting process, orange showed much higher bioaccessibility (>70%) for several phenolic components (catechin, procyanidin-B2, rutin, and epigallocatechin-gallate) than juice did. This suggests that fermented oranges may be a source of bioavailable phenolic chemicals, which may have positive effects on health (Barreto et al., 2022).

According to Kömürcü and Bilgiçli (2022), the inclusion of baker's yeast during Tarhana fermentation resulted in several modifications to the finished product (Cankurtaran Kömürcü & Bilgiçli, 2022). A rise in total phenolic content, a decrease in phytic acid, an increase in fat content, and an increase in antioxidant activity were among these alterations.

The Tarhana also saw color changes, texture softening, and enhancements in its capacity to absorb oil and foam. These changes imply that the inclusion of baker's yeast may have a variety of consequences on Tarhana's composition, texture, and functional qualities, affecting both sensory and nutritional elements.

The addition of yeast extract to lettuce dramatically increased total phenolics and chlorophyll without impacting other important elements such as vitamin C. This increase in phytochemicals improved lettuce's antioxidant and anti-inflammatory qualities, implying a safe and natural strategy to boost its health benefits. Notably, the highest outcomes were obtained with a single spray of 0.1% or 1% yeast extract (Złotek & Świeca, 2016).

A graphical presentation of the findings has been illustrated in Fig. 8. From the bar graph (A), Among the BACs produced by SC, beta glucan has the most published articles (6), followed by GABA and vitamins and minerals (3 each). The least published compounds are esters, peptides, and SCFA (1 each). From the bar graph (B), among health benefits of SC, antioxidant activity has the most published articles (15), followed by anti-inflammatory (6). The least published applications are skin health, cytotoxicity, and neurotransmitter (1 each). From the bar graph (C), among the food applications of SC, wine has the most published articles (11), followed by beer (8) and grain-based food products (6). The least published applications are emulsifier and milk kefir (1 each).

Overall, the bar graph suggests that beta glucan is the most researched bioactive compound produced by SC, and SC has the most potential health applications, particularly antioxidant activity. In the food industry, SC is mostly used in wine, beer, and grain-based food products such as bread.

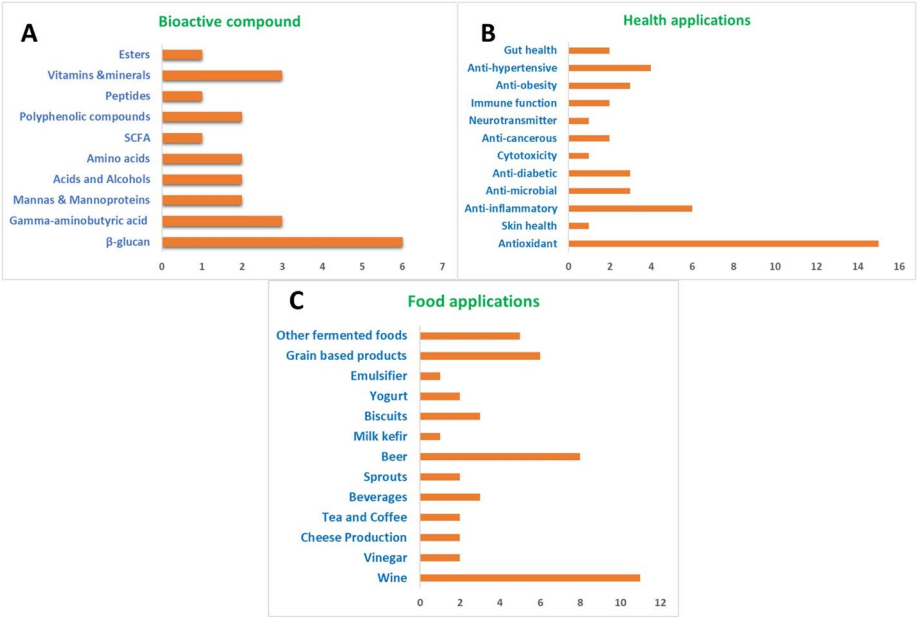


Fig. 8 Articles published on various Bioactive compounds produced by *Saccharomyces cerevisiae* under the scope of this studies (**A**). Articles published on various health benefits of *Saccharomyces cerevisiae* under the scope of this studies (**B**). Articles published on various food products feremented with yeast under the scope of this studies (**C**)

Table 1 Recent patents on bioactive compounds from *Saccharomyces cerevisiae*

Patent No.	Patent title	Country	Major outcomes of the invention	References
US10982295B2	Stain *SC* M 2,016,785 producing high concentration of β-phenylethanol and application thereof	United States	The yeast strain SC M 2,016,785, is capable of producing high quantities of β-phenylethanol (410–450 mg/L) in a variety of fermentation applications, including Baijiu, cooking wine, vinegar, and soybean sauce.	(Mao et al., 2021)
US10364444B2	*Saccharomyces cerevisiae* yeast strains and methods of use there	United States	This invention relates to ways of using SC yeast to produce ethanol from starch-containing substrates.	(Headman et al., 2019)
US11618889B2	Saccharomyces cerevisiae kwon P-1, 2, 3 which produce aldehyde dehydrogenase and glutathione	United States	A strain of yeast that produces both glutathione (GSH) and aldehyde dehydrogenase; in particular, SC Kwon P-1 KCTC13925BP, SC Kwon P-2 KCTC14122BP, and SC Kwon P-3 KCTC14123BP are strains of yeast that produce both glutathione and aldehyde dehydrogenase.	(Kwon, 2023)

Overall, these studies demonstrate the diverse effects of yeast-related ingredients, like baker's yeast and yeast protein extract, on the properties of various food products. These uses highlight the potential of yeast-derived components to improve the functional qualities and nutritional value of a variety of food matrices. Table 1 summarizes various patents granted on Bioactive Compounds from *Saccharomyces cerevisiae.*

3.4 Research problems, solutions, and the theoretical contribution of the study

In our systematic study, the potential of SC as a source of BACs for the development of functional foods and health benefits was thoroughly examined. It was found that a wide range of BACs, such as beta-glucans, mannoproteins, polyphenols, vitamins, and minerals, could be obtained from SC. These BACs have a number of functions that are important for the production of functional foods, including possible blood sugar management, antioxidant qualities that lower oxidative stress, and prebiotic activity that supports gut health. The wide range of health-promoting potential of BACs produced from SC was demonstrated by the results of the study. For example, one neurotransmitter found in this review, GABA, was noted to be critical for regulating brain activity, which may have therapeutic implications for treating neurological conditions. Moreover, it was shown that the β-glucans derived from SC promote the development of macrophages and dendritic cells, which are essential elements of the immune system. The effect of β-glucan on immunological function was observed to differ based on the size of the molecule, emphasizing the need for more research into this connection in the future. It was implied that they may be useful in the treatment of long-term illnesses like obesity, inflammation, and even neurological problems. The review also emphasized how adaptable SC is for fermenting different foods (cheese, yogurt, etc.), which is consistent with sustainable food production methods.

4 Challenges and future prospects, and interdisciplinary approach

4.1 Challenges

The utilization of SC for bioactive compound production holds tremendous promise for enhancing human health, yet it encounters multifaceted challenges that must be surmounted to fully exploit its potential. Key among these challenges is the issue of protein stability and folding, which significantly affects the efficiency of BAC production. Resource competition during production diminishes protein titers, exacerbated by selective pressures favoring non-producing cells and genetic variations. Consequently, this phenomenon results in diminished growth rates, biomass yield, and respiratory capacity, thereby hindering overall productivity. Addressing these challenges requires a comprehensive understanding of cellular responses to production burdens, which can be attained through omics-based approaches and the study of gene regulatory networks (Kastberg et al., 2022).

Additionally, metabolic bottlenecks within SC pose significant hurdles to efficient BAC production. Increased demands for energy, precursors, and redox-cofactors during protein production overload central carbon metabolism, further diminishing productivity. Alleviating these bottlenecks necessitates the optimization of metabolic pathways and the development of dynamic control systems to mitigate cellular burdens (Kastberg et al., 2022). Furthermore, genetic engineering techniques such as CRISPR-Cas9 hold promise for enhancing strain performance and improving overall production efficiency (Utama et al., 2021). In the context of specific BACs like β-glucan, SC faces challenges related to extended lag phases, pH fluctuations, and limited glucose availability. These factors significantly impact β-glucan yield and quality, hindering its potential as a viable production platform. However, advancements in fermentation process optimization and genetic engineering offer avenues for enhancing β-glucan production capabilities. Furthermore, exploring novel applications of β-glucan in various industries, such as food, pharmaceuticals, and cosmetics, could unlock its full potential and drive further innovation (Utama et al., 2021). Innovative techniques like biosorption offer promising solutions to enhance the concentration and bioaccessibility of BACs in SC. By acting as a sponge, SC can absorb valuable BACs like phenolic acids, thereby increasing their concentration and enhancing their health-promoting properties. However, scaling up biosorption techniques for industrial applications requires further development in cleaning and stabilizing biosorbent yeast. Additionally, understanding the specific mechanisms of biosorption and its impact on compound behaviour during digestion is crucial for maximizing its potential (Ribeiro et al., 2019).

4.2 Future prospects

Despite these challenges, SC holds immense potential as a platform for producing a wide range of health-promoting BACs. Its well-understood biology, established fermentation techniques, and Generally recognized as safe (GRAS) status make it an attractive candidate for industrial-scale production. Furthermore, advancements in genetic engineering and synthetic biology offer unprecedented opportunities for enhancing metabolic pathways and developing entirely new compounds (Chrzanowski, 2020). By addressing current challenges and harnessing the power of innovative technologies, SC can emerge as a versatile and invaluable tool for improving human health through the production of BACs.

This investigation of BACs produced from SCs creates intriguing new study directions. Further research into the unique properties of these BACs may result in the creation of novel functional foods and nutraceuticals that are suited to the treatment of particular medical conditions, such as diabetes or problems with the GI tract. Furthermore, it is essential to comprehend the underlying mechanisms via which SC-BACs exercise their beneficial effects on health. Finally, for SC-BACs to be used more widely in the food and health sectors, it will be crucial to investigate scalable and sustainable production techniques. Scientists can make a major contribution to the improvement of food science and human health by carrying out research in these areas and continuing to bridge the gap between fundamental science and practical applications.

4.3 Interdisciplinary approach

The humble baker's yeast, SC, has many uses in a wide range of fields, far beyond its reputation in food. To maximize its influence in a sustainable way, it is essential to comprehend its interdisciplinary links. The developing field of algal biofuels is one example of such a link. Research on the techno-economic viability of producing algal biodiesel (Maroušek et al., 2023a, b) emphasizes the need for mass cultivation techniques that are affordable in order for this biofuel to rival conventional sources. It's interesting to note that improving these techniques can help with SC production. Large-scale SC fermentation operations can benefit from the adaptation of techniques developed for effective algae growth, such as maximizing nutrient delivery and avoiding contamination, as these techniques ensure both industries' scalability and economic sustainability. Moreover, studies on the use of biowaste for fish feed in insect farming (Maroušek et al., 2023c) provide an insight into a viable biorefinery cycle. Although the study is focused on insects, SC can also benefit from this idea. Various sugars obtained from biomass, including agricultural waste streams, can be effectively used by SC. This capacity can be used to transform biowaste into useful biomass made of SC. Furthermore, in a closed-loop system, the leftover fermentation broth from the manufacture of SC may be used as a source of nutrients for the cultivation of algae. The multidisciplinary method incorporates SC with current waste management techniques to promote a more sustainable bioeconomy. The economics of processing food waste are improved overall and biogas production is accelerated by advances in nutrient management (Maroušek et al., 2020). A cooperative system can be built that maximizes resource usage and reduces waste formation by optimizing nutrient delivery for both the upstream biogas production stage and SC fermentation. The significance of robust and sustainable supply chains has been highlighted by the COVID-19 pandemic (Valaskova et al., 2023). SC is a viable option for localized and sustainable food and resource production due to its effective conversion of easily accessible biomass into useful products. Incorporating SC into an Industry 4.0 biorefinery model can help us construct a more robust and sustainable bioeconomy in the post-pandemic period.

Artificial intelligence, big data, and digital twins are some of the innovations that define the new sector of Industry 4.0 (Kliestik et al., 2023; Dvorský et al., 2023; Valaskova et al., 2024). These developments present great opportunities for optimizing SC production and integration within a sustainable biorefinery model. While big data analytics can optimize nutrient delivery and fermentation settings for optimal SC productivity. Similarly, AI-based predictive maintenance can reduce downtime in fermentation facilities. The complete

biorefinery process, including SC fermentation, waste valorization, and potential links to biogas production or nutrient recovery, can be modeled and optimized using digital twin simulations.

In conclusion, SC is a prime example of the effectiveness of multidisciplinary research. We can realize its full potential for a more sustainable and healthful future by comprehending its place in the larger framework of biofuel production, waste management, sustainable food systems, biogas generation, nutrient recovery, and Industry 4.0 integration. Investigating these links further could lead to the development of innovative goods and procedures that minimize environmental effect and optimize resource efficiency while supporting a circular bioeconomy.

5 Conclusion

The untapped potential of *Saccharomyces cerevisiae* was revealed by this systematic review. Thirteen distinct bioactive molecules that SC produces were found, along with thirteen possible health advantages such as gut health to chronic disease prevention. Furthermore, 13 distinct fermentable food products are produced by SC, demonstrating its extraordinary adaptability and encouraging sustainable food production practices. These BACs have the potential for producing novel functional foods that will meet the increasing market for goods that promote health. By bridging the gap between research and practice, this study establishes the foundation for future developments in the application of SC for better health and a more sustainable food system.

Abbreviations

ABTS	2,2-azino-bis-3-ethylbenzothiazoline-6-sulphonic acid
ACE	Angiotensin-converting enzyme
ATP	Adenosine triphosphate
BAC	Bioactive compounds
BCD	β-cyclodextrin
BGCC	Beta-glucan-chitin-chitosan
BRF	Brown rice flour
BRYE	Black rice yeast extract
BRYE	Brewer's yeast extract
BS	Buckwheat sprouts
DPPH	2,2-diphenyl-1-picrylhydrazyl
EPS	Exopolysaccharide
EV	Extracellular vesicles
FGUBF	Fermented and gelatinized Urad bean flour
FRAP	Ferric reducing ability of plasma
GABA	Gamma-aminobutyric acid
GRS	Generally recognized as safe
HMG	Hydroxymethylglutaryl
HT	Hydroxytyrosol
MP	Mannoproteins
PEF	Pulsed Electric Fields

PP	Potato peel
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta- Analyses
RSA	Radical Scavenging Activity
SC	Saccharomyces cerevisiae
SCFA	Short-chain fatty acids
SO_2	Sulfur dioxide
TNF	Tumour Necrosis Factor
VOS	Visualization of Similarities

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Data availability All data generated or analysed during this study are included in this manuscript.

Declarations

Ethical approval The authors declare that the submitted manuscript is original and unpublished elsewhere, and that this manuscript complies with the Ethical Rules applicable for this journal.

Financial interests The authors declare they have no financial interests.

Competing interests The authors have no competing interests to declare that are relevant to the content of this article.

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ORIGINAL PAPER

Exploring Biopolymer for Food and Pharmaceuticals Application in the Circular Bioeconomy: An Agro-Food Waste-to-Wealth Approach

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Abstract

Globally, a substantial quantity of agricultural food waste and byproducts that contain significant bioactive chemicals are produced, particularly across the whole supply chain. Reducing food waste and byproducts is the initial choice to mitigate environmental issues and contribute to economic and societal well-being. Despite the implementation of many policies and the availability of numerous management methods to utilize agricultural food wastes, these wastes continue to be generated on a yearly basis. Researchers have identified numerous types of waste materials that can be used as substrates in the manufacturing of biomaterials. Conversely, there has been a growing emphasis on using agro-food waste, namely waste from fruits, vegetables, and fatty products, to produce various types of biopolymers. Biopolymers comprise gelatin, xanthan gum, cellulose, collagen, Polyhydroxyalkanoates and other chemically related substances. This review focuses on significant biopolymeric materials synthesized from agricultural food waste and their prospective applications. This work also addresses the difficulties and possibilities associated with the creation of sustainable biopolymer-based composites derived from agri-food waste biomass through a closed loop strategy and circular economy. The study's findings suggest that incorporating agricultural biomass into the production of biopolymer-based composites holds significant promise for improving environmental sustainability. The extensive aggregated data can aid academics in addressing and resolving the problems related to food waste and the depletion of fossil fuels.

Jibanjyoti Panda, Awdhesh Kumar Mishra,Yugal Kishore Mohanta are contributed equally.

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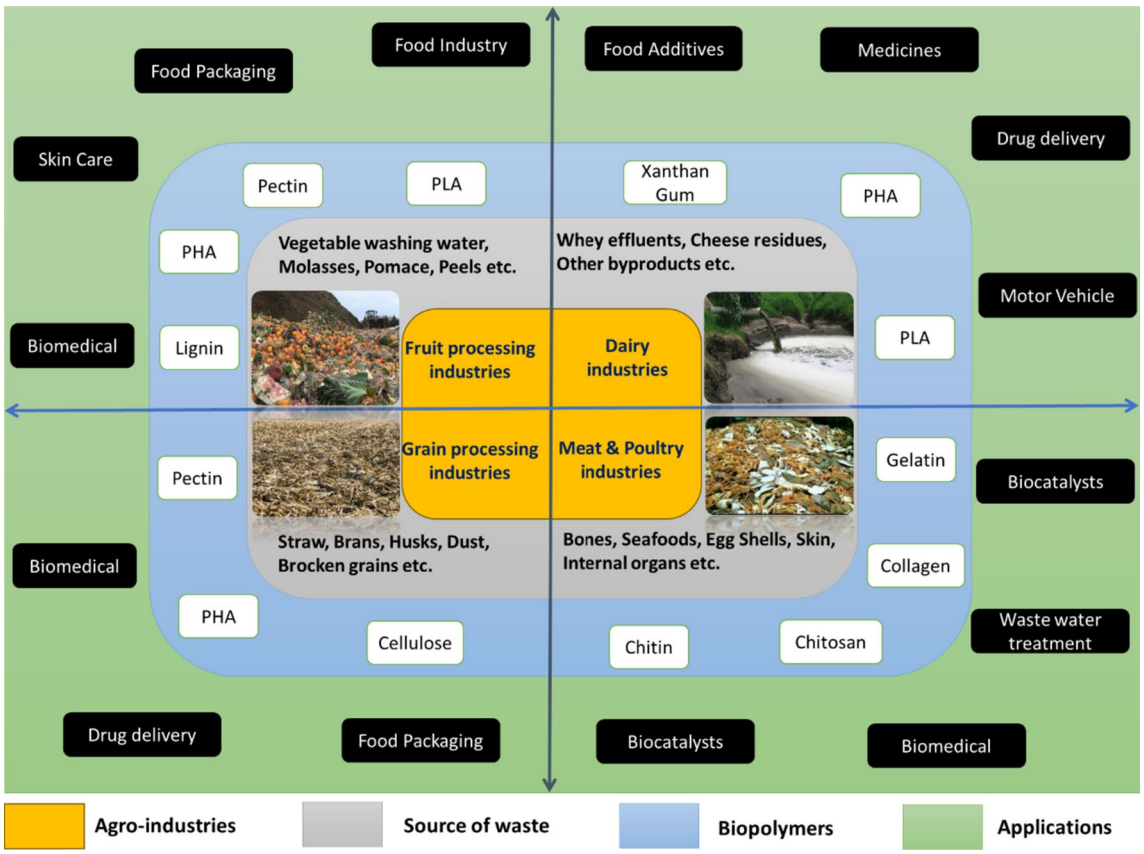
Graphical Abstract



Keywords Biopolymer · Food waste · Waste valorization · Bio-economy · Sustainability

Abbreviations

ACLs	Anterior cruciate ligaments
CAGR	Compound annual growth rate
DDS	Drug delivery system
ELPs	Elastin-like polypeptides
EPS	Exopolysaccharide
ER	Extended-release
EU	European Union
MC	Micro-cellulose
mcl-PHA	medium-chain-length polyhydroxyalkanoates
MMC	Mixed Microbial Cultures
MSCs	Mesenchymal stem cells
NC	Nano-cellulose
P (3HB - co -3HV)	Poly(3-hydroxybutyrate-co-3-hydroxyvalerate)
P (3HB – co -4HV)	Poly(3-hydroxybutyrate-co-4-hydroxyvalerate)
P(3HB-co-3HHx)	Poly(3-hydroxybutyrate-co-3-hydroxyhexanoate)
PDO	Polydioxone
PGA	Poly glycolic acid
PHA	Polyhydroxyalkanoates
PHB	Polyhydroxybutyrate
PHBHV	poly(3-hydroxybutyrate-co-3-hydroxyvalerate)
PHD	Polyhydroxydecanoate
PHHx	Polyhydroxylhexanoate
PHO	Polyhydroxyoctanoate
PHV	Polyhydroxyvalerate
PLA	Polylactic acid
PVA	Polyvinyl alcohol
SDG	Sustainable Development Goals
ZnO	Zinc oxide

Statement of Novelty

The novelty lies in utilizing agricultural food waste to produce biopolymers and addressing challenges in creating sustainable composites through a closed-loop strategy and circular economy.

Introduction

In light of the critical shift towards a circular bioeconomy, it is essential to conduct a thorough investigation into the potential uses of biopolymers within the food and pharmaceutical sectors. By placing particular emphasis on the "Agro-Food Waste-to-Wealth" framework, which entails the conversion of agricultural residues into valuable biopolymers, the primary obstacle is to effectively exploit the complete capabilities of these sustainable substances. Despite the increasing attention given to the utilization of biopolymers, there are still knowledge gaps concerning the practical implications, scalability, and optimization of this methodology within the framework of the circular bioeconomy. Based on the latest findings from the Food and Agriculture Organization (FAO), it is disheartening to note that a staggering 1.3 billion tons of food go to waste annually. Food waste is a pressing issue that stems from various sources within the food industry and post-harvest agro-processing. This issue not only poses a significant threat to the environment but also affects both pre-market and post-market sites [1, 2]. In the realm of sustainable agriculture, it is noteworthy to mention that the beverage industries have emerged as significant contributors, accounting for approximately 26% of the overall food waste. Following closely behind is the dairy industry, which is responsible for approximately 21% of food waste, while the fruit and vegetable industry contributes around 14.8%. Additionally, the cereal industry plays a role, contributing approximately 12.9% to the total food waste [3]. The management of these organic wastes typically involves their disposal at designated landfill sites or their utilization in the production of nutrient-rich compost. However, it is important to consider the potential for recycling processes to derive value-added products from these food wastes, as this not only supports waste recovery but also has the potential to generate higher financial returns [4].

Biopolymers have emerged as a highly intriguing product derived from agro-food wastes due to their remarkable characteristics, such as biodegradability and compostability, biocompatibility, and their bio-based origin. Various methods, such as extraction or fermentation, effectively achieve the synthesis of biopolymers from agro-food wastes. Depending on the specific requirements, one can carry out these processes with or without pre-treatment. Solid-state fermentation employs it to get fermentable sugars, which are essential for the production of biopolymers [5].Biopolymers can be identified based on their origins. Polysaccharides (such as cellulose derivatives, chitosan, and starch) are natural sources of biodegradable polymers, while aliphatic polyesters, poly-anhydrides, poly (alkyl-cyanoacrylates), poly-amino acids, phosphorous-based polymers, and acrylic polymers are synthesized in the laboratory. Polyglycolide, polylactic acid, polylactide-co-glycolide, polycaprolactone, polybutylene succinate, polypdioxanone, polycarbonate, polyamides, poly(esteramide)s, polyurethanes, polyanhydrides, and vinyl polymers are all petroleum-based polymers that break down naturally. Microbial fermentation can produce two examples of biodegradable polymers: poly(hydroxybutyrate-co-hydroxyvalerate) [P(3HB-co-3HV)] and poly(hydroxybutyrate). There is a wide variety of possible applications for biopolymers derived from food waste due to their many desirable features. These include biodegradability, biofunctionality, biostability, biocompatibility, and an extensive range of chemical and mechanical characteristics. These sectors include healthcare, food and beverage, construction and transportation, pharmaceutical and medical, and information technology [4, 6, 7].

In order to address the dearth of knowledge, an extensive bibliometric investigation was conducted on the production and applications of biopolymers derived from food waste, utilizing the global scientific literature. Agro-food, waste, diary waste, oil waste, fruit and vegetable wastes, and biopolymer are a few examples of the keyword data points that were gathered from close to 250 articles. VOS viewer, a cluster-based software, was used to do the analysis. This software was used to create, analyse, and display scientific mapping in cluster format based on the co-occurrence of terms, normalizing the results using the "Association strength" method (Fig. 1) [8].

The objective of this study is to fill in these knowledge gaps and harness the revolutionary capabilities of biopolymers obtained from agro-food waste. By doing so, it enables the creation of novel approaches that support the environmentally responsible advancement of circular bioeconomy within the food and pharmaceutical industries. Therefore, the principal aim of this study is to provide a significant contribution to the progression of eco-conscious and sustainable economic system. The objective will be accomplished through the promotion of the utilization of biopolymer-based composites as a viable alternative to traditional materials in several prospective domains. The findings of this study have the potential to make a significant contribution to the advancement of sustainable efficiency of resources materials and methods, as well as to the further development of our knowledge in the field of biocomposite research.

Agro-food Waste

Types and Origin

Global population expansion, rapid urbanization, and changing customer demands have challenged food processing

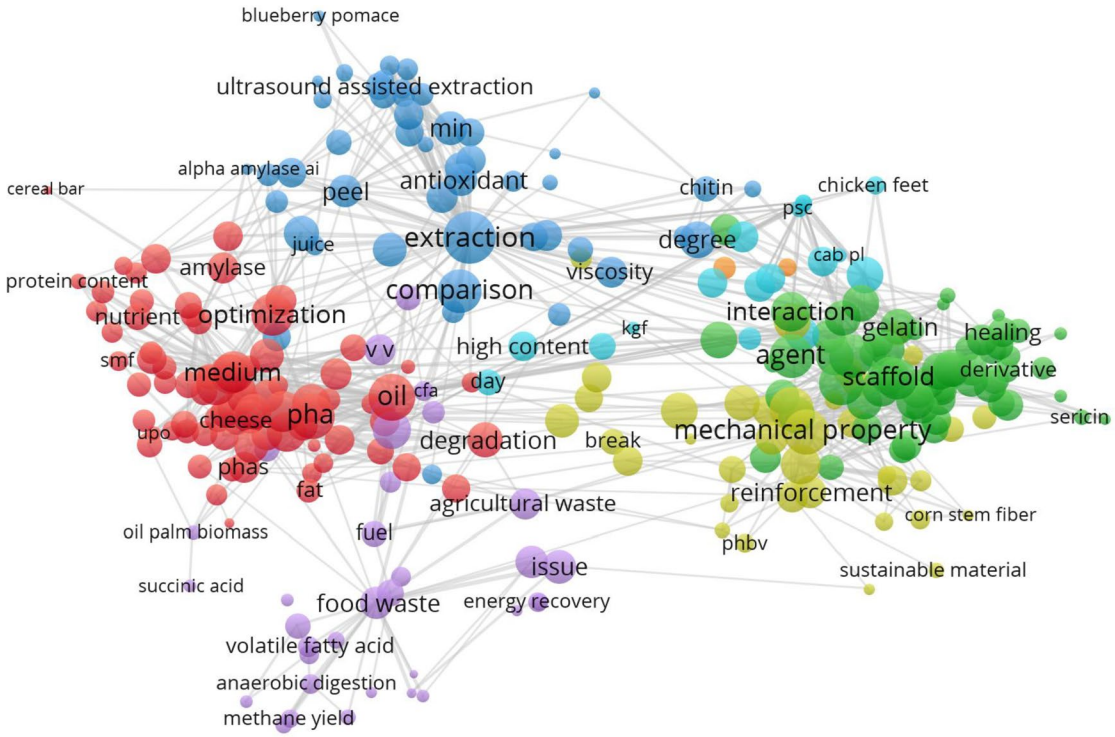


Fig. 1 Co-occurrence network of biopolymer production and application from agro-food waste

companies. These industries handle large amounts of plant, animal, and agricultural residues. A sustainability consultant's duties include addressing issues of improper waste management and the accumulation of natural trash. This worrying condition threatens human civilization's health and lifespan. During harvest or slaughter, "food loss" is sometimes used to describe waste. Production, harvesting, transportation, industrial processing, and consumption are the main causes of food waste [9]. A large part of organic waste comes from farms and food processors. Harvest and agro-industrial waste, as well as abandoned fruits and vegetables, make up a large component of agricultural waste [10, 11]. Food processing produces a lot of cereals, legumes, fruits, vegetables, dairy, meat, eggs, and seafood waste. Also consider how commercial and residential kitchen trash affects waste management [12]. Strategic repurposing of agro-food waste may help solve environmental deterioration and waste management. Utilizing this waste material to create a variety of bioproducts (biopolymer) could potentially address these issues. This method lets us use agro-food waste to make biofuels, xylitol, xylooligosaccharides, bioplastics, and organic acids. Additionally, it has applications in the fields of food production, medicine, biosensors, textiles, plastics, cosmetics, water treatment, drugs, and even data storage devices [6]. Adopting this sustainable technique can tackle waste management concerns while also creating a society that is more environmentally friendly and resource-efficient. Harnessing the potential of non-consumable agro-food wastes is essential for waste management and sustainable development. Strategically implementing cutting-edge technologies and new methods can achieve this [13, 14]. Different types of biopolymer/bio-composites are obtained from several sources of agro-food waste are exhibited in Table 1.

Global Generation of Agro-food Waste

Food waste can be attributed to several stages of the food supply chain, encompassing production, distribution, and consumption. The quantity of food waste generated exhibits variability throughout different regions of the world, owing to diverse factors such as climatic conditions and topographical characteristics. One of the Sustainable Development Goals established by the United Nations is to achieve a 50% reduction in food waste by the year 2030. According to the Food Waste Index study conducted by the United Nations Environment Program in 2021, it was estimated that over 931 million tons of food were discarded globally in the year 2019. Approximately 40% of the global food supply is lost or wasted within the distribution system. The numerical values exhibit significant variation across different geographical locations and various stages of the production process. A significant proportion of food is lost or wasted prior to and during harvest in poor nations (low-income countries), while in affluent nations, it occurs primarily during eating.

Table 1 Biopolymers/bio composites from different source of agro-food waste

Sources	Products	References
Apple pomace	Pectin	[15]
Banana pseudo-stems	Bio oil	[16]
Barley husk	Arabinoxylan	[17]
Blueberries waste	Anthocyanin	[18]
Seafood and eggshells	Collagen, gelatine, chitin/ chitosan, PHA	[6]
Bread waste	succinic acid	[19]
Hazelnuts, husk, malt dust, straw, and bran	PHA	[6]
Calcium alginate	Bioethanol	[20]
Carrot discard juices	Bioethanol	[20]
Cheese whey	P (3HB – co -4HV)	[21]
Cheese whey	Xanthan gum	[22]
Cheese whey	PHA	[23]
Chicken feet	Collagen	[24]
Corn bran	Pullulan	[25]
Crude palm kernel oil	P (3HB - co -3HV)	[26]
Date byproduct (Deglet-Nour)	H2, CH4	[27]
Date molasses and seed oil	P(3HB-co-3HHx)	[28]
De-oiled Jatropha waste	H_2	[29]
Fish oil	P (3HB – co -4HV)	[30]
Food waste	H_2	[31]
Food waste	Reducing sugar	[32]
Food waste	Volatile fatty acids	[33]
Food waste	Bio-ethanol	[34]
Food waste (canteen)	Methyl esters	[35]
Waste from fruits and vegetables, dairies, and animal feed	Bio gas (methane)	[36]
Fruit and vegetable waste	H_2 and CH_4	[37]
Fruit waste	methane	[38]
Gac peel	Carotenoid and Antioxidant	[39]
Gold kiwifruit pomace	Pectin	[40]
Grape marc	Flavanols	[41]
Grape stalk	Phenol	[42]
Groundnut oil cake (GOC)	Lipase	[43]
Guava peels and cashew bagasse	single cell protein	[44]
Jackfruit peel	Pectin	[45]
Milk whey	Xanthan gum	[46]
Molasses (sugarcane)	PHA	[47]
Spent coffee grounds, bagasse, molasses	PHA	[6]
Mung seed waste	Polyphenol	[48]
Sesame oil cake, coconut oil cake,, and oil cake.	α-Amylase	[49]
Oil palm pressed waste	Succinic Acid	[50]
Olive fruits wastes	Single cell protein	[51]
Orange peel	Invertase	[52]
Orange peel	α-Amylase,	[53]
Orange peel	Single cell protein	[54]
Orange peel waste	Bioethanol	[55]
Orange peel waste	Lactic acid	[55]
Orange peel waste	Acetic acid	[55]
Papaya, watermelon, and banana peel	Single cell protein	[56]

Table 1 (continued)

Sources	Products	References
Pastry and cake waste	Succinic acid	[57]
Pineapple waste	single cell protein	[58]
Prawn shell	Chitosan	[59]
Rice bran	α-Amylase	[60]
Soybean bran, rice bran, wheat bran, and black gram bran	α-Amylase	[61]
Waste seed coat from red sword bean	Polyphenol	[62]
Sisal waste	Pectin	[63]
Soy waste	Single cell protein	[64]
Specnt coffee grounds (SCG) oil	PHB	[65]
Spelt bran and hull	Arabinoxylan	[66]
Spent coffee ground	polysaccharides, phenolics	[67]
Sugar beet juice	PHB	[68]
Sugarcane bagasse	PHB	[69]
Sugarcane vinnase and molasses	PHB	[70]
Tomato processing waste	Pectin	[71]
Various food waste	Biohythane	[72]
Vegetable peel, pomace, molasses, beet pulp	PLA, PHA, pectin, Xanthan gum, cellulose, and lignin	[6]
Waste cooking oil	Biodiesel	[73]
Waste cooking oil	mcl-PHA	[74]
Peeled citrus and wheat bran	Methylene pectin esterase	[75]
Whey	PHA	[76]
Whey lactose	PHA	[77]
Whey permeate	PHA	[77]
Whey, hydrolysate and cheese Residue	PHA, xanthan gum	[6]
Yam peel	Single cell protein	[78]

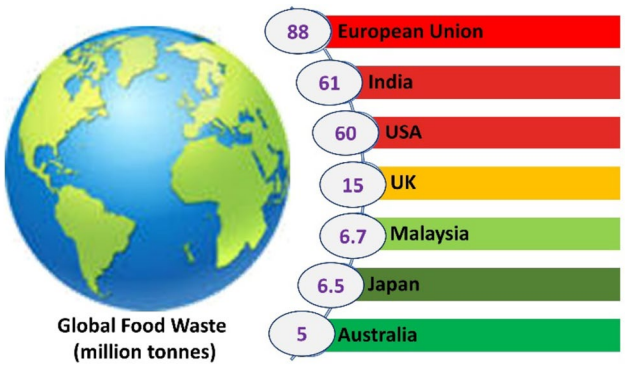


Fig. 2 Pictorial data of food waste around the world

The European Union (EU), India, and the United States are the leading global contributors to waste generation (Fig. 2).

It is noteworthy that both industrialized nations, such as the European Union and the United States, as well as developing countries like India, are actively involved in the generation of waste materials. China is another rising country with a key role to play in the current food waste situation. A material flow analysis, for instance, indicated the nature and volume of various sorts of waste. Wheat waste accounted for 38% of total trash, whereas milk waste accounted for 4%. Tomatoes wasted the most during production and marketing, at 28% and 25%, respectively, whereas wheat wasted the most during post-harvest handling and storage, at 56%, processing and packaging, at 36%, and consuming, at 48%. Milk, apples, tomatoes, pork, and wheat were the most often discarded foods by consumers. Soybeans were the most wasteful food item during processing and packing, whereas freshwater fish were the most wasteful during production [79]. One study found that the food and beverage consumption stage in 2016 wasted over 4.47% of China's grain production [80]. These nations are obligated to optimize the utilization of waste products in order to reduce their bioburden. Both of these entities have the capacity to enact measures that could reduce the burden of the aforementioned waste [6, 81, 82].

Composition of Agro-food Waste Resource in Synthesis of Biopolymers

Agro-food wastes, which can be from either plants or animals, are the leftovers after the cultivation and preparation of a wide variety of agricultural products. Spoilage can also happen during the packing and distribution phases of the supply chain [83]. A wide range of resources, from leaves and seaweed to animal skins and corn stover, can be used to make biomass. Biomass can also be obtained from waste materials such as bran, gut, husk, bones, and animal trimmings. Additionally, processed end products such as bagasse can be a source of biomass [84]. Biopolymers vary in composition depending on the organism from which they originate. A past study into the chemical make-up of various forms of agro-food waste is summarized in the Table 2 below [85]. In addition, a prior study found that corn stover is made up of 11.7% lignin, 31.10% hemicellulose, and 40.67% cellulose. Many different types of carbohydrates, including hemicellulose, cellulose, and lignin, as well as minerals like phosphate and calcium, can all be found in wheat straw [86]. Three to fifteen% protein, one to three% fat, seven to thirty-eight% minerals, 50% carbohydrates (particularly alginate, cellulose, and fucoidan), and eighty to ninety% water make up the bulk of brown seaweed by dry weight [87]. When sugarcane is refined, it creates bagasse, which is a waste product. Carbohydrates are abundant in it, with cellulose accounting for 32–48%, hemicellulose for 25–32%, lignin for 19–24%, raw extractive components for 5–9%, and ash for 3% [88, 89]. The chemical make-up of common agro-food wastes is listed in Table 2 as a percentage by weight [85].

Source of Biopolymer from Agro-food Waste

Fruit and Vegetable Waste

Food waste has increased due to increased production to fulfil consumer demand, limited infrastructure, and worldwide management issues. Fruit and vegetable waste accounts for 42% of food product waste [90]. The improper disposal of peels, seeds, stalks, leaves, roots, pomace, and remaining fruits and vegetables from homes, cafeterias, and food processing enterprises can harm humans and the environment. Minerals, vitamins, enzymes, fibers, protein, carbs, oil, bioactive chemicals, and polyphenols are abundant in food waste [91, 92]. One-third of the world's food supply is wasted annually due to spoilage or poor storage. Horticultural products (fruits and vegetables) make up 60% of this loss. India produces 86.602 million metric tons of fruit and vegetables annually [93]. Thus, the amount of trash disposed of on city outskirts has increased to 5.6 million tons, rising every day. According to the Food and Agriculture Organization (FAO), India wastes over 40% of its fruit and vegetable produce. The Food Corporation of India has disclosed that the proportion of waste in their whole production varies between 10 and 15% [94]. As the production of fruits and vegetables is increasing progressively, the waste generated should not surpass the yearly fruit and vegetable production. According to the report from the Ministry of Agriculture and Farmers Welfare in 2023, the expected fruit and vegetable output for the years 2022–23 is 108.34 and 212.91 million tonnes, compared to 107.51 and 209.14 million tonnes in the years 2021-22, respectively. However, the production and elimination of these wastes have resulted in significant economic losses and health issues due to their noxious smell,

Table 2 Chemical composition of various types of agro-food waste (% w/w)

Agro-food wastes	Cellulose	Lignin	Total solids (%)	Hemi-cellulose	Moisture (%)	Ash (%)
Barley straw	33.8	13.8	–	21.9	–	11
Coffee skin (g/100 g)	23.77	28.58	–	16.68	–	5.36
Corn stalks	61.2	6.9	97.78	19.3	6.40	10.8
Cotton stalks	58.5	21.5	–	14.4	7.45	9.98
Oat straw	39.4	17.5	–	27.1	–	8
Orange peel	9.21	0.84	–	10.5	11.86	3.5
Pineapple peel	18.11	1.37	93.6	–	91	–
Potato peel waste	2.2	–		–	9.89	7.7
Rice straw	39.2	36.1	98.62	23.5	6.58	12.4
Sawdust	45.1	24.2	98.54	28.1	1.12	1.2
Soya stalks	34.5	19.8	–	24.8	11.84	10.39
Sugar beet waste	26.3	2.5	87.5	18.5	12.4	4.8
Sugarcane bagasse	30.2	13.4	91.66	56.7	4.8	1.9
Sunflower stalks	42.1	13.4	–	29.7	–	11.17
Wheat straw	32.9	8.9	95.6	24.0	7	6.7

discharge of leachate into the surroundings, and contamination of landfills [95]. Composting, landfilling, cremation, and livestock feed have environmental impacts. Most people believe vegetable and fruit waste disposal solutions reduce waste and help produce higher-value commodities. A technologically advanced and innovative waste management plan is needed to produce ecologically sustainable, economically efficient, and widely marketable value-added products.

Due to their high concentration of important biopolymers, the potential of waste from fruits and vegetables has been investigated. Thermophilic bacterial strains can produce polyhydroxybutyrate (PHB) only from waste carrots [96]. The feasibility of employing Pseudomonas strains for the manufacture of medium-chain-length polyhydroxyalkanoates (mcl-PHA) from substrates produced from waste frying oil and fruit pomace, specifically those of the apricot, grape, and cherry [97]. Using white grape pomace as a substrate, *Pseudomonas putida* KT2440 was shown to grow well and efficiently produce mcl-PHA [98]. Bacillus spp. are able to synthesize copolymer PHA and homopolymer from volatile fatty acids obtained via hydrolysis of pea shells, potato peels, onion peels, and apple pomaces. Grape pomace that has been treated with enzymes is used by *Cupriavidus. necator* to synthesize PHA [99]. Using apple pulp waste as a substrate, the *Pseudomonas citronellolis* strain NRRL B-2504 was able to produce mcl-PHA [100]. Research on the global market for bio-based polymers predicts that the PHAs market will expand to $98 million by 2024 [101]. According to the adage, "necessity is the mother of invention," so the world's growing population, the persistence of hunger, problems with food waste and pollution, and the effects of the economy's ups and downs could trigger a period of revolutionary innovation in the food industry [4].

Dairy Waste

The byproduct generated by the dairy industry in the course of milk product manufacturing is commonly referred to as dairy waste. Dairy industry waste contains a wide variety of materials, including fats, oils, grease, minerals, and phosphates, as well as soluble organic compounds, suspended solid particles, and trace levels of organic chemicals. Past research has shown that these building blocks are necessary for biopolymer production [102–104]. PHB is the name of the main biopolymer that is created when bacteria are recovered from dairy waste. The bioconversion of dairy industry wastes into polyhydroxyalkanoates (PHA) has been proposed using three different methods. There are only a few microorganisms known to directly convert lactose to polyhydroxyalkanoates (PHA) [105, 106]. Some of these organisms *are Hydrogenophaga pseudoflava, Thermus thermophilus, Pseudomonas hydrogenovora, Bacillus megaterium*, and engineered strains that have genes that break down lactose. Whey can also be converted into sugars that various microbes can use by using either chemical or enzymatic processes to hydrolyze lactose into glucose and galactose. The fermentation of lactose into lactic acid is the first step of a two-step bioconversion method [107]. PHA-producing bacteria next convert the lactic acid to PHA. For industrial production of polyhydroxyalkanoates (PHAs), using mixed microbial cultures (MMC) to enhance complex substrates is a realistic method for generating high yields [108]. In order to maximize PHB synthesis, buttermilk is used as a carbon source during the fermentation process (at pH 7, at 37 °C, and 150 rpm). Additionally, buttermilk is the most affordable way to use microbes isolated from dairy wastes to make microbial polymers [109]. .

Additionally, dairy waste can be bioprocessed to obtain EPS and food texture is often improved by adding extracellular polymeric molecules. Whey and its derivatives can make many bacterial extracellular polymeric compounds [108]. The bacterial strains *Pseudomonas, Azotobacter chrococcum, A. vinelandii, Lactobacillus delbrueckii subsp. bulgaricus, L. rhamnosus, Xanthomonas cucurbitae, X. campestris, Rhizobium radiobacter S10, Zunongwangia profunda*, and *Sphingomonas paucimobilis* produce EPS from dairy wastes better [110]. The lactose-negative *Rhodotorula acheniorum* strain and *Lacticaseibacillus casei* 91 strain were co-cultured to generate high EPS. While promising, microorganism-derived EPS may be too pricey. Using cheap raw materials and improving production can alleviate this restriction [111]. Some of the many useful qualities of these chemicals are emulsifying, biocatalytic, gel-forming, and anticancer. As a result, they're seen as practical alternatives to polymers made from petroleum [108]. Polylactic acid (PLA) and polyhydroxyalkanoates (PHAs) are two examples of biopolymers that exhibit plastic and mechanical properties comparable to petroleum-based plastics. The disposable nature of these materials also makes them useful in the medical field, as well as in the food and clothing industries [107].

Oily Waste

Despite rising production and population growth, oily food waste remains one of the world's most pressing issues. Currently, the 10–40% oil content of food waste adds a layer of complexity to waste management. Environmental and human health are both at risk from the use of waste oils due to their carcinogenic, teratogenic, and mutagenic properties. The deteriorating and undesirable components in waste oils present these risks [112, 113]. When oil is heated, it is oxidized by free radicals. As a result of this reaction, the structure of the oil is altered, and acrylamide and 4-hydroxy-2-alkanal are produced [112, 113]. In addition, the oxidation of unsaturated fatty acids during cooking results in the production of trans fatty acids. This change increases the

stability of trans fatty acids [114]. China produces 5 million metric tons of waste cooking oil annually, contributing to the global total of 16.5 million metric tons [115, 116]. The edible oil industry generates oil waste during several reaction phases of refining, including degumming, neutralization, deodorization, bleaching, and oxidative or hydrolytic rancidity. India wastes about 300 million barrels of oil annually due to food preparation. Oil meal and de-oiled cake, high-quality proteins, are produced annually by the edible oil industry at 350.9 million tons. Waste cooking oil was recycled into animal feed, garden compost, and soil amendment [117].

Polyhydroxyalkanoates can be produced from waste frying oil from the potato chips and chicken frying industries. Polyhydroxybutyrate (PHB) concentrations are higher in *Cupriavidus necator* fermentations with waste frying oil than in pure vegetable oil. The use of nitrogen sources and increased free fatty acid levels allow *C. necator* to better absorb fatty acids into the fatty acid oxidation cycle. As a result, this metabolic pathway boosts PHB production [118, 119]. Bacteria from soil and slaughterhouse waste can develop on used cooking oil, commercial lard, and tallow. This suggests that these substrates may create more biopolymers per cell dry mass [120]. Oily wastewater can supply carbon and nitrogen to microorganisms. Polyhydroxyalkanoates (PHA) are derived from organic acids derived from residual oil and lignocellulosic components in anaerobic wastewater resulting this renewable and cost-effective carbon source [121]. Polyhydroxybutyrate (PHB) is made from residual glycerol byproducts of palm oil, waste frying oil, castor oil, jatropha oil, and whey [122]. Oil mill effluent can be utilized for synthesis of PHA and copolymer poly(3-hydroxybutyrate-co-3-hydroxyvalerate) (PHBHV) [123]. Polyhydroxybutyrate was generated using sunflower meal wastes and a bacterial strain that used crude glycerol as a carbon source [124]. The presentation of a technologically effective biopolymer synthesis from home and industrial oily waste Because oils are instantly introduced to fermentation media as a carbon substrate, no pretreatment is required [125]. Figure 3 depicts an overview of various agro-food waste and alternatives for converting them into biopolymers.

Agro-food Waste Derived Biopolymers

The majority of the world's population relies on plants as a primary or secondary source of nutrition each year. After the harvesting process of fruits and vegetables, a substantial quantity of organic waste or crop residue remains. Animal feed or field incineration are the most common uses for this waste [126, 127]. Wood dust, bagasse, rice husks, and the inedible portions of fruits and vegetables are only some of the examples of agricultural leftovers and trash that are discussed in this paper as prospective raw materials for the manufacturing of biopolymers because of their sustainability. The goal of turning these agricultural byproducts into biopolymers is to combat plastic and environmental degradation. In what follows, we'll take a look at a few of the more prominent biopolymers that can be manufactured from food scraps.

Cellulose

The most prevalent natural polymer on Earth, cellulose, accounts for approximately half of photosynthesis-based organisms' biomass and is essential to plant cell walls. Photosynthesis turns carbon dioxide and water into glucose in green plants. Its chemical reactivity is greatly affected by cellulose's structure, making it a versatile precursor. Cellulose monomers can generate diverse biopolymers and useful materials. For many uses, cellulose-based polymers can replace petroleum-based polymers. The use of cellulosic

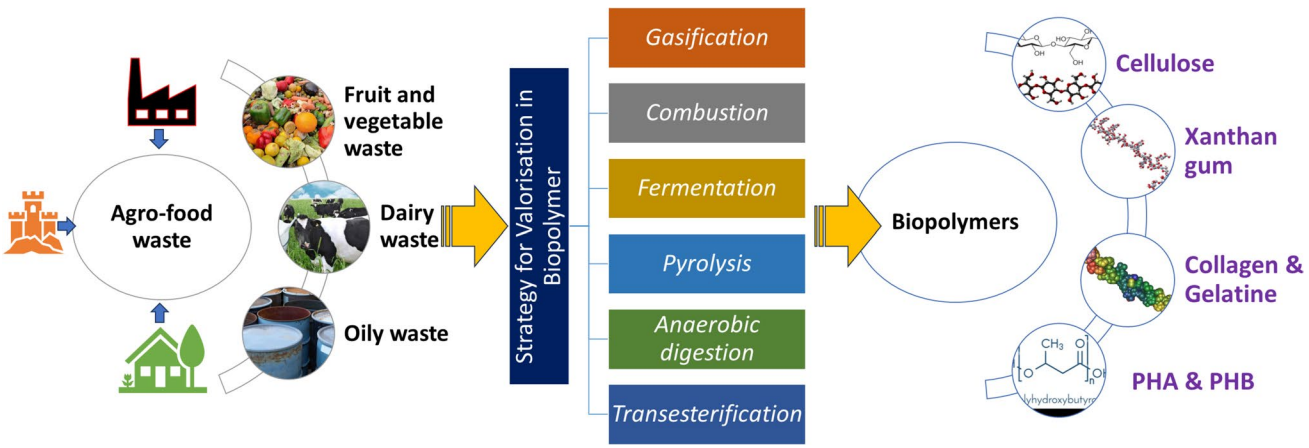


Fig. 3 An overview of different agro-food waste and options for converting these into biopolymers

resources like natural fibers, nanocellulose, and cellulose derivatives seems promising in bio composites [128]. The effects of bamboo cellulosic fibers in cement composites were examined in this study. In cement composites, adding the right amount of fibers increases fracture toughness and impact energy absorption [129]. Peanut oil cake cellulose extraction for filler has been studied. Natural fiber composites' thermal and mechanical qualities may improve using this method. A mechanical property analysis of these composites showed good results [130]. Cellulose fiber composites have lower strengths than glass fiber and carbon fiber composites due to the incongruity between the hydrophobic polymer matrix and the hydrophilic natural fibers and their lower temperature tolerance [131]. Cellulose fibers lose their mechanical characteristics when wet. Thus, chemical grafting and physicochemical treatments are needed to change cellulose fiber surfaces. Chemical treatment of organic material fibers eliminates non-cellulose elements, improving heat stability and mechanical qualities. Cellulose biopolymers can be matrix materials in cutting-edge biotechnological applications [132]. These materials can improve bio-composite characteristics as fillers. To reinforce biodegradable polymer composites, natural cellulose fibers are replacing talc and glass fibers.

Xanthan gum

Xanthan gum, a heteropolysaccharide, is an important biopolymer that is mostly produced by a species of the genus Xanthomonas called *Xanthomonas campestris*. Around thirty thousand tons of this substance are produced each year worldwide, and used extensively in the food, pharmaceutical, and petrochemical industries for the synthesis of xanthan gum. Cheese whey, spent malt grains, and citrus wastes are just some of the agro-food byproducts that have been found to be useful for the production of xanthan gum [6, 133]. In a study, it was observed that a mixture of jackfruit seed powder, citric acid, peptone, K_2HPO_4, and KH_2PO_4 was utilized for the production of xanthan gum. The ultimate product yield was calculated to be 51.65 g/L [134]. One common byproduct of potato chip manufacturing is potato waste, which is rich in carbohydrates. This trash has been converted into biopolymers like xanthan gum with the use of enzyme hydrolysis. Xanthan gum has been synthesized using the *X. campestris* bacterial strain (NRRLB-1003) by a number of fermentation techniques, including submerged, solid-state, and semi-solid-state fermentation. Potato peels have been used as a substrate replacement in several techniques. Nonetheless, studies have shown that xanthan gum production is lower in submerged state fermentation compared to solid and semi-solid fermentation techniques [135]. Using *Xanthomonas campestris* pv. manihotis ISBF 1182 strains and potato peel as an alternative substrate, a different study looked into how xanthan gum could be made through submerged and semisolid fermentation. Silva et al. [136], looked into whether it was possible to get xanthan gum out of potato peel and found that the semisolid fermentation method gave a higher yield than the submerged method (20.9 g/L, 48 h vs. 2.03 g/L, 72 h). The economic importance of xanthan gum, which is widely used in the food industry, cannot be overstated. The high cost of using pure sucrose as a substrate complicates industrial Xanthan fermentation. *X. campestris* can metabolize the glucose, sucrose, vitamins, and minerals present in food scraps like carrot and pumpkin peels [137].

Collagen

The biopolymer polysaccharides are the most common in all known forms of life. However, collagen is a protein-based biopolymer that is abundant in the skins and bones of mammals like cattle and pigs. Fish waste (scales, bones), eggshells, and chicken processing scraps are just a few of the animal byproducts from which collagen is extracted [138]. Tendons, ligaments, skin, and the organic component of bone and teeth account for over 90% of the body's total collagen. Collagen type I, commonly known as fibrillar collagen, is a controlling agent for the tensile strength of bone's extracellular matrix [139]. Acetic acid, NaCl, and pepsin are used to hydrolyze non-collagenous proteins at cross-linking sites. Pepsin concentration, acetic acid concentration, and hydrolysis time are the most important factors in determining collagen yield [140]. It has been claimed that seafood-derived waste can be used to produce collagen-based food ingredients, which can then be used as part of a biological solution to recycle the trash [141]. Chicken skin is treated with 0.5 M acetic acid, 1% pepsin, and 20% ethanol to extract collagen; the skin is then washed with 0.1 N NaOH and 20% ethanol to remove fat and non-collagenous protein, yielding 10 to 12% Type-I collagen [142]. In a study, it was shown that a mixture of 0.45 M NaCl, 0.5 M acetic acid, and 0.1% pepsin resulted in a yield of 49.15% for pepsin-soluble collagen, 14.50% for acid-soluble collagen, and 1.15% for salt-soluble collagen while processing poultry waste to extract collagen [143]. Applications in the pharmaceutical, biological, leather industry, cosmetics, and food industries are extensive [6].

Gelatin

Gelatin, a biopolymer obtained by the denaturation process of collagen, is widely employed in diverse applications. In addition to traditional extraction sources, gelatin can be derived from collagen-rich waste and byproducts produced by industrial operations, including poultry and cattle slaughterhouses, as well as the fishing sector [144]. The commercial sourcing of gelatine predominantly relies

on porcine and bovine animals, constituting around 95% of the total supply. The substance under consideration is commonly acknowledged as the principal constituents of the exoskeleton observed in several marine zooplankton species, like corals, jellyfish, shrimp, crabs, prawns, and lobsters. Furthermore, it is also found in the cellular walls of fungi and the exoskeletons of insects [145]. The manufacture of L (+)-lactic acid by the amylolytic lactic acid bacterium *Enterococcus faecium* K-1 utilizes gelatinized starchy waste (GSW) as a substrate. GSW is derived from rice noodle factories and acts as a suitable medium for this purpose [146]. Solid wastes produced by fish consist of various by-products such as bones, scales, and skins, which possess a significant amount of collagen and account for around 75% of the total body weight. The investigation of employing these waste materials for the extraction of diverse products, such as gelatin, has been examined in the food and pharmaceutical sectors [147]. The byproducts resulting from the processing of seafood are considered to be a substantial and noteworthy source of valuable molecules, including biopolymers and bioactive compounds. The potential use of biopolymers, including gelatin in the creation of sustainable and long-lasting food packaging materials. These materials might potentially be enhanced with antibacterial agents or antioxidants [148].

Polyhydroxyalkanoates (PHA) and Polyhydrooxybutyrate (PHB)

The biodegradable polyesters known as polyhydroxyalkanoates (PHAs) are produced through bacterial fermentation [149]. To ensure their own survival, the bacteria produce polyhydroxyalkanoates (PHAs) by accumulating PHA granules through an unbalanced growth process during fermentation. Around 300,000 monomers make up the biopolymer class known as short chain polyhydroxyalkanoates (PHAs). Polyhydroxybutyrate (PHB), polyhydroxyvalerate (PHV), and their copolymers fall within this category. In this specific subset, PHB has received a lot of attention and is widely used since it is a polymer with notable mechanical performance features [150]. Polyhydroxyalkanoates (PHAs) with medium chain lengths are generated from monomers with 6–14 carbon atom chains. Polyhydroxydecanoate (PHD), polyhydroxyoctanoate (PHO), and polyhydroxylhexanoate (PHHx) are all chemicals referenced in the book. The synthesis of polyhydroxyalkanoates (PHA) and polyhydroxybutyrate (PHB) through bacterial fermentation involves the utilization of several microbial species, including *Alcaligenes*, recombinant *Escherichia coli*, *Agrobacterium*, *Rhizobium*, *Azospirilum*, *Aeromonas*, *Pseudomonas* sp., *Cupriavius*, *Azotobacter*, *Rhodobacter*, *Bacillus*, and *Sphaerotilus* [151, 152].

Before agro-food waste can be processed into polyhydroxyalkanoates (PHA), it must undergo pre-treatment. This critical step, which requires digestion of the sample matrix, can be performed chemically or biologically. Polyhydroxyalkanoate-producing bacteria then use the available carbon resources to synthesize PHA. Recognizing that waste substrates used in PHA production have varying nitrogen and phosphorus content is important because these elements must be present in sufficient amounts to support PHA synthesis. Overabundance of any one of these components may stymie the procedure [153, 154]. A few examples of agro-industrial wastes are whey from the dairy business and molasses from the sugar industry. In addition to carbohydrates, vitamins and trace minerals can also be found in molasses. According to Joyline and Aruna [155], *Bacillus megaterium* and *Pseudomonas fluorescens* are two of the best substrates for PHA synthesis. PHA was isolated from ragi husk and sesame oil cake using the *B. megaterium* strain Ti3 [156]. Validation of batch fermentation for PHA generation using a mixed microbial culture isolated from corn straw, a byproduct of the food sector Verdini et al. [157], state that the use of such technologies has the potential to increase the competitiveness of producing biopolymers from agri-food waste. Wang et al. [158], look into how lignocellulosic crop residues, lipid type agricultural wastes, and other agro-industrial wastes like molasses and whey can be turned into PHA. These materials serve as important resources and serve as a platform for future scaling-up and industrial uses of PHA synthesis. Many plant foods, such as fruits and vegetables, contain sugars that converted into PHAs by fermentation. Cucumber, peach, onion, plum, and melon waste were used in the production of PHA, as were the byproducts of industry made from apricot, yellow apple, pear, tomato, and red apple. According to Costa et al. [159], the best feedstocks for the synthesis of PHA are residues produced from red apples and melon. Packaging, including containers and films, coatings, pharmaceuticals, and the medical industry, are just a few of the many fields where PHAs are widely used.

Environmental, Economic, and Life Cycle Assessment (LCA)

The majority of nations adopt a linear approach to production, utilization, and disposal, depleting resources in the process of product development with limited consideration for recycling. This is true for bio-based and chemical economies alike. An improved approach would be to repurpose the remains into something of value, thereby transforming the linear trajectory into a cyclical one in which materials are put to good use once more. A circular bioeconomy is characterized by its objective of preserving the value of

materials over an extended period of time, as opposed to their rapid conversion into refuse [10, 11]. The objective is to develop a system that produces no pollution and has a reduced environmental footprint. To achieve this, however, requires inventive research into methods to transform each byproduct of a given process into a marketable product [12]. Within the framework of waste management, biorefinery, and sustainability, Fig. 4 depicts bioprocessing of food waste in order to produce of biopolymer.

The Life Cycle Assessment (LCA) is a method that assists us in determining what is and is not sustainable, with an emphasis on environmental friendliness. Examining sustainability from all three perspectives—environmental, economic, and social—is necessary to fully comprehend it. LCA looks at every step of a product's life cycle, from obtaining raw materials to getting rid of trash [24]. It is widely utilized in many different industries to select environmentally friendly materials and systems. It examines elements such as the possibility for eutrophication, acidification, toxicity, global warming, resource depletion, ozone depletion, and pollution production. It is important to consider not only environmental impacts but also economic and social ones. Life-cycle costing (LCC) is used for the economic aspect of this [33].

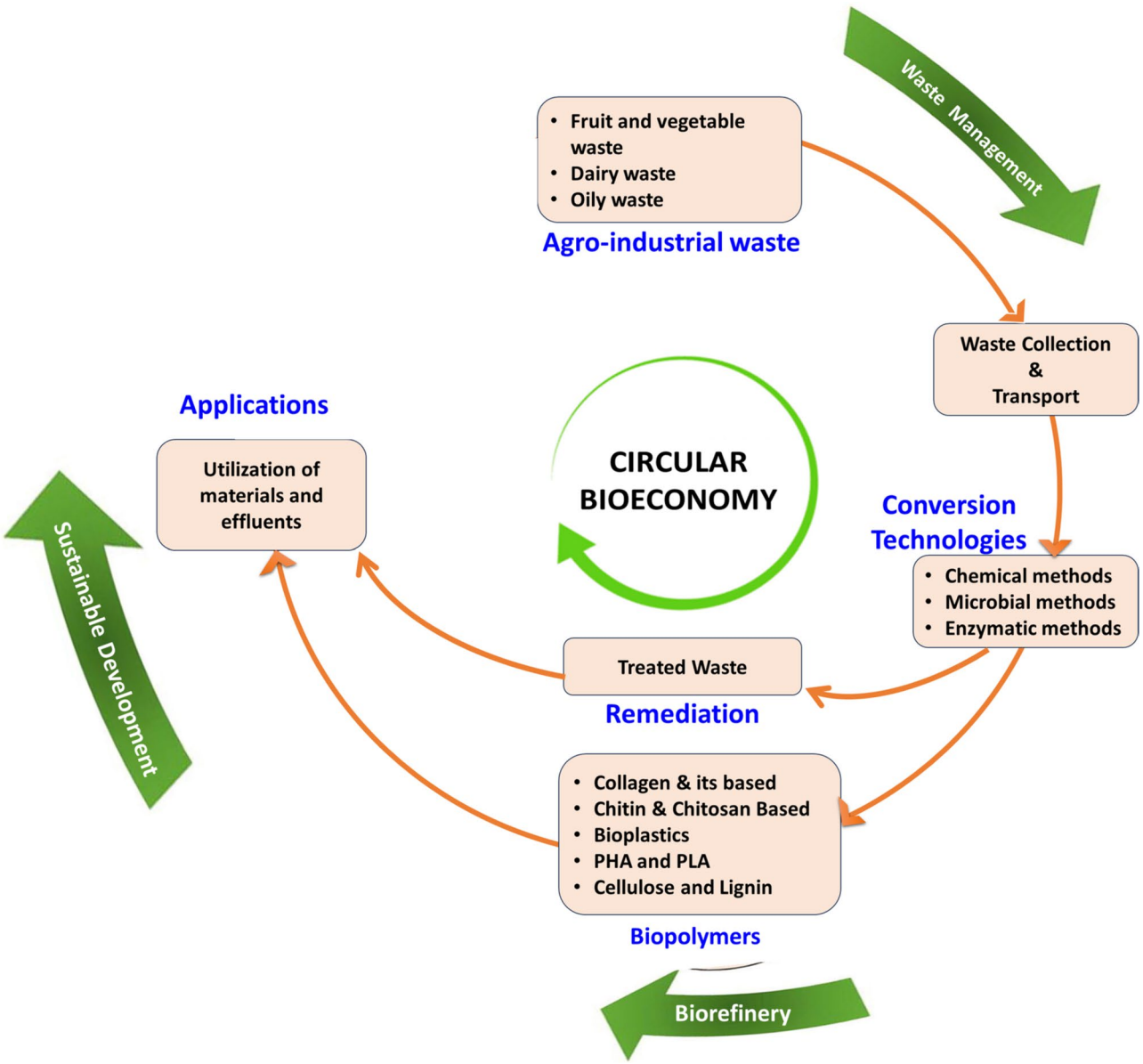


Fig. 4 Bioprocessing of food waste in the production of biopolymer under the context of waste management, biorefinery, and sustainability

Impact Assessment

Despite being in its early stages, the use of LCA methodology in biopolymer development has already been widely used in several industries as an effective tool for selecting materials and systems to achieve a more sustainable production process. Cumulative energy demand, International Life Cycle Data System (ILCD), and Eco Indicator 99 are among the numerous environmental impact assessment tools that have been established. The methods can be classified into two main categories: midpoint methods and endpoint methods. The use of midpoint approaches allows for precise calculation of very specific impacts by employing a weighted total of exchanges with the measured natural environment. The midway impact group consists of freshwater usage, climatic change, natural land use, ozone layer depletion, and freshwater eutrophication. The endpoint techniques employed a weighted summation technique to combine numerous midpoint data in order to produce more comprehensive impact records [160].

Munoz et al. (2018) conducted the first cradle-to-gate life cycle evaluation (LCA) of chitosan manufacturing. The goal of the study was to analyze primary data from two supply chains located in Europe and India, which differ greatly in terms of raw materials and production sites, in order to identify key areas of concern. The animal feed market is impacted by the utilization of shrimp shells as primary materials, which enhances its credibility across several impact indicators [161].

The utilization of protein residue as a fertilizer has a substantial impact on the release of greenhouse gases and ammonia. Conversely, the environmental impacts, particularly related to the production of heat and electricity from carbon-based sources, are mostly influenced by energy consumption in Europe and China [160]. By employing crab shells as the main material for decomposition, the release of ammonia, which contributes to acidification, is minimized. The diversion of shrimp shells from the animal feed market through their application has a significant impact on the Indian supply chain in terms of indirect land use change (iLUC). In contrast, the European supply chain is minimally affected by iLUC, as the crab shells have no impact on the animal feed market. This study provides valuable insights into the global environmental impacts of chitosan production conducted by two companies. Furthermore, it sets a benchmark for future studies that examine the production of chitosan utilizing different raw materials and manufacturing methods, including bioengineering [160, 162].

Applications and Global Market of Biopolymer

People have utilized agriculturally produced natural fibers for various applications, including canvas, textiles, and building construction materials. These agricultural byproducts, including straw, weeds, sawdust, and manure, have found valuable applications as fuels, fertilizers, and building materials. Despite the longstanding employment of natural fibers, the emergence and subsequent commercialization of synthetic fibers, notably carbon, glass, and aramid fibers, at the early and mid-twentieth centuries resulted in a lessened predisposition towards natural fibers across many purposes. These modified biopolymers find applications in fields as varied as medicine, the auto industry, wound healing, water purification, metal recovery from mining waste, the food processing sector, drug delivery, cooling systems, sanitation supplies, and personal care items (Table 3).

Potential Applications

Biopolymer for Wound Healing

The primary function of biopolymers in wound healing is as vehicles for transporting therapeutic agents to the injury site. The natural wound healing properties of some biopolymers, however, include antibacterial, sticky, analgesic, wound healing factor promotion, reduced scarring, and so on. Due to blood loss and subsequent problems, wound healing is a crucial and potentially life-saving process following injury. In the absence of care, infections in wounds can spread and weaken the body to the point where amputation becomes necessary.

The immune system has been shown to detect collagen as a helpful protein during wound healing [200]. Because of its distinctive fibril patterns, collagen is a potent stimulator of cell growth and differentiation. High-porosity collagen sponges can facilitate faster recovery by fostering the development of new tissue. Collagen serves as a scaffold for transporting healing agents such as growth factors and antibiotics to the burn wound site. Inflammatory cells assault the sponge's porous structure, and fibroblasts migrate into the wound, establishing the framework for the quick development of new epithelial layers and granulation tissue. Also, if you implant a collagen sponge, it will degrade over the course of three to six weeks, and then your body's own fibroblasts will manufacture type I collagen to fill in the void [201]. Collagen hydrogels deliver cells, anaesthetics, growth hormones, and other medications that promote wound healing. Researchers

Table 3 Potential applications of some common biopolymers obtained from agro-food waste sources

Sources	Applications	References
Agar	Processed meat products	[163]
Agarose	Regeneration of skeletal tissues, encapsulation of fibroblasts and kidney cells	[164]
Alginate	Regenerative medicine, Tissue engineering	[165]
Alginate	Confectionary milk-based desserts, jellies	[166]
Carboxymethylcellulose	Confectionary, Salad dressing	[167]
Carrageenan	Skeletal tissues regeneration, cell delivery system	[168]
Collagen	Coatings to the surfaces of cell culture plates and uncomplicated gels	[169]
Cellulose	Applications in the biomedical field, including wound dressing systems, drug delivery, and tissue engineering.	[170]
Corn starch (whist corn and rice fiber shells)	Mechanical properties (including hardness, flexural strength, impact response, and tensile and compressive strength) and thermal stability were augmented with an increase in the proportion of rice husk and walnut shell.	[171]
Starch and husk from maize	The addition of maize husk to the composite resulted in improvements to its crystallinity index, tensile strength, and Young's modulus.	[172]
Elastin	Encapsulation of cells, soft-tissue reconstruction, and orthopedics.	[173]
Fibrin	Coagulation, wound repair, and tumor development, Surgical adhesive, sealant, and hemostatic agent	[169]
Fibronectin	Wound healing, bone regeneration and cardiac repair	[174]
Gellan	Frozen foods, sugar syrups	[175]
Guar gum	Jams, syrups, and pie fillings	[176]
Gelatin	Food packaging	[144]
Gum karaya	Frozen foods, cheeses	[177]
Hemicellulose	Pet foods	[178]
Hyaluronic acid	Wound healing in the cutaneous and corneal layers, joint repair and lubrication.	[179]
Keratin	Skin regeneration and corneal tissue engineering.	[180]
Pectin	Icings and glazes	[181]
PHAs	Drug delivery systems	[182]
PHBV (potato pulp)	Reduced elastic modulus and a moderate loss in tensile characteristics were noted.	[183]
PHBV (stem wheat)	The flexural modulus exhibited an upward trend as the fiber fraction increased.	[184]
PHBV/Paunch	There is no discernible alteration in rigidity when paunch is added. Mechanical properties comparable to buffel grass biocomposites were achieved with a pulp content of 30% by weight.	[185]
PLA (pork bone powder)	The tensile and bending properties of the ready-made composite were enhanced.	[186]
PLA (spent coffee grounds)	The elongation at break of the composite is enhanced by the inclusion of coffee grounds. Reduced rigidity and tensile strength.	[187]
PLA (wood biochar and Sewage sludge biochar)	Biochar increased composite stiffness and water absorption. Sewage sludge biochar composites outperformed wood biochar in mechanical and thermal properties.	[188]
Polyglactine (PLA-PGA)	Artificial vessels, ligaments, fasteners, pins, orthopedic fixation, and sutures comprise orthopedic fixation.	[189]
Polylactides (PLA)	Tissue regeneration matrix, orthopedic fixation, fixation, screw and pin, artificial ligament and tendon.	[190]
Poly-lysine	Encapsulation of drugs, biosensor, bactericides	[191]
Polypropylene (corn cob)	The maize cob was thermally resilient at high temperatures, decreasing processing damage. Corn cob raised flexural and elastic moduli and decreased tensile strength and ductility.	[192]
Polyspartates	Medication encapsulation, suture, artificial skin	[193]
Pullulan	Protective coating	[194]
Silk fibroin	Wound healing, regenerative medicine, and tissue bioengineering	[195]
Silk-fibroin	Medical regeneration, wound healing, and tissue bioengineering	[195]
Starch	Packaging of Fatty Foods	[196]

Table 3 (continued)

Sources	Applications	References
Starch	Spinal cord injury treatment, bone and cartilage regrow	[99, 197]
Xanthan gum	Beer	[198]
Xanthan gum	Use in food, textile, oil industries, medical, sector as drug delivery, tissue engineering and oil agent.	[199]

have proposed collagen-based hydrogels loaded with mesenchymal stem cells (MSCs) as a treatment for cutaneous wounds [200]. Collagen is not only an important component of wound dressings but is also crucial in the development of tissue-engineered skin substitutes. Type I collagen's excellent strength and biocompatibility make it suitable for direct skin replacement. Collagen implants promote the growth of epithelial and granulation tissue, speeding up the healing process. Collagen-based treatments like Apligraf®, a bioengineered skin substitute, are effective in treating ulcers caused by conditions including diabetes and venous insufficiency.

As a biopolymer, gelatin can regulate and treat wound exudate from partial- and full-thickness wounds. Wound dressings often contain gelatin and other biopolymers due to its hemostatic characteristics. Pfizer's Gelfoam® is a sterile compressed sponge used for hemostasis. This gelatin material absorbs blood up to 45 times its weight, making it ideal for wound dressings and hemostatic sponges. Gelatin, pectin, and carboxymethyl cellulose make up hydrocolloid dressing DuoDerm® [200]. Hydrocoll® and Pharmacoll®, gelatin-free hydrocolloid dressings, were created due to ethical and religious concerns about mammalian gelatin. Besides its use in skin tissue engineering and wound delivery of growth factors and antimicrobials, gelatin has been studied in combination with other biopolymers like chitosan and poly (vinyl alcohol) [202]. Tissue engineering and cell transport technology should improve biological wound healing methods.

Products that highlight chitosan's versatility as a biomaterial have recently emerged, demonstrating the material's growing popularity. Chitosan has been used for a variety of purposes due to its antibacterial and antifungal qualities, as well as its role in wound healing [203, 204]. Chitosan membranes manufactured using solvent casting techniques have various intended uses, including wound healing. Researchers have conducted studies on using chitosan hydrogel and nanoscale zinc oxide (ZnO) as potential wound dressings [205]. Activated platelets stuck to the composite bandages, demonstrating their superior hemostatic and antimicrobial properties. Researchers have already looked into adding silver to chitosan hydrogel composite bandages. These bandages have shown some interesting properties, including a high swelling ratio, antimicrobial properties, controlled biodegradation, and better blood clotting abilities [206].

The use of pectin-based substances in wound healing therapy has a long history. Pectin's bioactivity has led to its historical use in wound healing therapy. Pectin increases interleukin-1 production by macrophages and promotes B cell proliferation [207]. Pectin is a great material for wound dressings because it is hydrophilic and can remove exudates while still maintaining an acidic pH to prevent the growth of bacteria and fungus [208]. According to research, pectin concentration in dressings varies from less than 10% in the second stage of wound healing to 40% in the first stage [200]. Pectin's prospective uses in tissue engineering, medication delivery, and wound dressing have generated considerable interest. Pectin provides a variety of benefits in various formulations, including hydrogels, films, scaffolds, and nanoparticles [209, 210]. The growing number of research organizations and the improving quality of the research are expected to result in the commercial availability of innovative pectin-based wound healing biomaterials in the near future.

Biopolymer in Tissue Engineering

Biomaterials cover a diverse array of materials, including polymer composites, nanocomposites, hydrogels, bioceramics, and biocompatible pure materials. Healthcare and tissue engineering techniques focus on improving the overall well-being of individuals through disease treatment, diagnosis, and prevention. Based on available research, biopolymers have demonstrated considerable potential as a viable material for tissue engineering owing to their advantageous biochemical and biophysical properties. These attributes render them appropriate for utilization in both in vivo and in vitro environments [211].

The special features of elastin-based polymers make them desirable for use in tissue engineering. Elastin is a protein found in many body tissues [212]. It imparts elasticity to ligaments, blood vessels, skin, and lungs. Skin and blood arteries are elastic; therefore, biomaterials need to be as well. Elastin-like polypeptides (ELPs) are multifunctional brain-directed drug transporters. In order to administer therapeutic medications to specific parts of the central nervous system, ELPs increase the biocompatibility and stability of

polymeric structures and make them amenable to intranasal delivery [213]. When it comes to soft tissues like arteries, ligaments, lungs, and skin, elastin-based biomaterials are seeing increased usage in tissue engineering. Over the course of their lives, humans and animals alike repeatedly contract and release these muscles and tendons. One of the most stable proteins is tropo-elastin, the primary protein in elastin and elastin-like peptides, with a half-life of 70 years.

Many functional scaffolds require gelatin, a biopolymer having biological, mechanical, and kinetic properties that is important to the scaffold's function [214]. This material's use is enhanced when electrospun with other natural or synthetic polymers. Biocompatibility makes gelatin nanoparticles a promising tool for regenerating damaged brain tissue. Adding gelatin to nanoparticles on PLA/acetate scaffolds improves cell viability. Gelatin-chitosan hybrid scaffolds aid in both cell proliferation and neurite outgrowth. A versatile biomaterial, collagen can regenerate, heal, or restore injured organs, tissues, or anatomical structures. The formulations of gelatin-polymeric hybrid material, which regulates the release of bioactive substances, conduct electricity, and boost mechanical properties. Potential applications for this combination include engineered neural and cardiac tissue. The conductivity measurements of this composite material are especially noteworthy because of the presence of polyaniline and carbon-based nanosubstrates. In tissue engineering, gelatin has low mechanical strength, poor heat stability, and rapid disintegration [215, 216].

Biomedical researchers have found numerous uses for alginate, which include drug delivery, cell culture substrates, and wound healing. Researchers have successfully used tissue engineering in various contexts, such as regenerating blood vessels, cartilage, repairing bones, the pancreas, muscle, the liver, and some peripheral nerves [217, 218]. Alginate-based materials have limited utility in tissue engineering due to their weak mechanical properties and quick breakdown. Alginate-based materials have been the subject of extensive clinical and pre-clinical research to determine their efficacy in this field [219]. In the context of tissue regeneration, alginate-derived materials have advantageous features as scaffolds for drug and cell carriers, as reported by [220].

Keratin-based polymer hydrogels can protect and maintain injured nerves, which improves tissue regeneration in a mouse model of peripheral nerve injury [221]. Due to its biocompatibility, biodegradability, and non-immunogenicity, keratin is a promising biological substrate [222]. The pliable structure and biological properties of keratin enable cell development and adhesion, while also allowing for easy processing and manipulation [223]. This biomaterial aids Schwann cell invasion and development, making it the first effective brain tissue engineering biomaterial. Keratin hydrogels can heal severe nerve injuries due to their biodegradability and ability to stimulate axonal ingrowth and neural cell adhesion. Researchers mixed keratin with petroleum-based polymers to form an electro-spun material that enhanced biocompatibility and mechanical qualities for glial cell proliferation, adhesion, and in vitro viability [211]. The PVA/keratin nano-fibrous scaffold used in tissue engineering enhances glial cell proliferation and in vitro viability. Keratin-loaded hydrogels accelerate neuron regeneration by increasing axon density and electrophysiological recovery time [224].

Medical Implants

The utilization of biopolymer-based implants represents a noteworthy advancement in the realm of inventive techniques and implant design for the purpose of tissue or organ regeneration and repair. Numerous biopolymers have gained recognition for their utilization as medical implants. Silk is widely utilized in the fabrication of synthetic implants. The raw silk produced by a silkworm consists of a central fibroid composed of silk fibroin, which is surrounded by a sericin protein coating that exhibits adhesive properties [225]. Recent scientific investigations utilizing precisely characterized silk fibers and films derived from silkworms have provided insights into the remarkable mechanical strength and biocompatibility of silk fibroin fibers. This research has demonstrated that silk fibroin fibers exhibit exceptional resistance to mechanical forces and are compatible with both polylactic acid (PLA) and collagen materials, both in laboratory settings (in vitro) and within living organisms (in vivo). The thermodynamically stable sheet structure of silk fibroin is attributed to the presence of robust hydrogen bonding and Van der Waals interactions. By the utilization of the patient's adult stem cells and silk material to fabricate a wire rope matrix intended for the creation of autologous tissue-engineered anterior cruciate ligaments (ACLs) [226]. The utilization of sericin-modified and composite materials has been observed in the development of biodegradable biomaterials, biomedical materials, functional membranes, fibers, and textiles [227]. PLA-PGA copolymer orthopaedic implants are increasingly popular. Surgeons use compression-molded copolymers to repair fractures and correct skeletal deformities with plates and screws. Copolymers can also scaffold cartilage growth. Copolymers of PLA and PGA are preferred over homopolymers for several reasons, including biocompatibility, non-toxicity, and controlled degradation rates [228]. In vascular surgery, PLA and PET-braided corrugated vascular prostheses restore blood flow to injured arterial segments. The framework absorbs the PLA, while the other biocompatible yarn provides mechanical support. The lab at Fangueiro also makes ligaments out of PLA, PGA, and PDO [229].

In addition to this, most of the body's supply of hyaluronic acid is located in the gums and periodontal ligaments. Typically, researchers and scientists alter hyaluronic acid to improve its resistance to degradation, viscosity, flexibility, and hydrophilicity [230]. Dental-bone substitutes for bone regeneration can be made using freeze-drying techniques and materials including hyaluronic acid-gelatin hydrogel polymers, tricalcium phosphate, and biphasic calcium phosphate ceramics. The biopolymer and bio-ceramic scaffold worked together to help osteocytes grow bones very quickly and safely, and they also kept the tissue from collapsing [231]. Alginate hydrogel showed promise for osteo- and adipo-differentiation in vitro [232]. In addition, it can serve as a scaffold for dental stem cells. The mechanical strength and cell adhesion of pure alginate are, however, quite weak [233]. A developed bioactive glass with zinc and magnesium-reinforced alginate networks. This reinforcement enhanced the biological, mechanical, and antibacterial properties of alginate networks. Biopolymers containing bioactive glass particles may prove useful in dental care, as demonstrated here [234].

Pharmaceutical Application of Biopolymer

Pharmaceutical tablets use microcrystalline cellulose granules as an excipient. The grains stick together, smooth out, and then break down. Microcrystalline cellulose's fiber structure expands when exposed to water, and this expansion is what experts believe causes pills to disintegrate and burst. Adding powdered cellulose to emulsions and suspensions acts as an absorbent, dispersant, and stabilizer. Cellulose derivatives have the potential to modify pharmacological solubility and gelation, opening up new avenues for drug delivery. Micro-cellulose (MC) and nano-cellulose (NC) are modified cellulose derivatives for long-term drug administration [235]. Cellulose and its derivatives are utilized in the pharmaceutical sector for various purposes, including long-lasting solid dosage forms, osmotic drug delivery systems (DDS), thickening and stabilizing agents, fillers in solid dosage forms, binders in the granulation process, taste masking agents, and extended-release (ER) and muco-adhesive drug delivery systems [236].

Pharmaceutical formulations utilize starches to transport medications and other bioactive substances. Active compounds are transported by chemically modified carbohydrates. Certain starches are suitable for bone repair and replacement because of their high digestibility [236]. Medical materials and pharmaceuticals can benefit greatly from amylose and its derivatives. Making safe medical suture threads and filaments is one example of these abilities. Surgeons use amylose sponges due to their high absorption rate. Amylose-iodine compounds have antibacterial properties that make them highly efficacious against gram + ve and gram -ve microbes. Amylose sulfate is also effective in treating stomach ulcers. Carboxymethyl amylose, facilitates antibiotic lymphatic system infiltration, making it suitable for parenteral administration [236].

Biopolymer in Biomedical and Pharmaceutical Packaging

Researchers apply alginates, a type of natural polysaccharide, in biomaterials for various purposes such as the food sector, water purification, biomedicine, and packaging [237]. Alginates find application in dentistry as a slow-release calcium salt and for encapsulation, tissue engineering scaffolding for ligament repair, and other purposes [238]. The pharmaceutical industry utilizes pure alginates to provide chemistry-based stability or dispersion. The high mechanical and barrier properties of the material protect the active compounds in alginate-based edible coatings, maintaining their efficacy [239]. These coatings often contain garlic oil, which is antibacterial. To improve paper coatings, one can fortify alginates with starch and calcium. The rheology is enhanced because of the uniformity of the bulk and coating [240]. With their unique physicochemical properties, alginates have attracted scientific attention for their potential use in biomedical wound care, particularly hydrogels. Biomedical engineering can benefit from the use of alginate-based materials due to their biocompatibility [241]. Wet-spun fibers have excellent absorbency for calcium and salt, making them ideal for creating highly absorbent dressings. The bioactive chemicals in fibers can be immobilized with alginic acid, silver, or zinc or stimulated with these metals to create antimicrobial fibers. The 99-nm alginate-quaternary ammonium complex nanoparticles created by ionic gelation are what give cotton textiles their antibacterial qualities. Antibacterial activity persists after 30 washes, indicating that these fibers may be non-leaching antimicrobials [242]. Researchers now have more options thanks to the development of modern dressings that are sterile, antibacterial, hypoallergenic, haemostatic, extremely absorbent, and biocompatible. Medications with special mechanisms for incorporation are possible. Tapes, knits, non-wovens, and composites are all examples of packaging textiles [243]. A growing body of evidence indicates that lignin is an essential building block of hydrogels, particularly for use in the pharmaceutical and medical industries [244]. A wide variety of companies manufacture lignin and cellulose, the two most common natural polymers. Dressings reduce pain and discomfort and absorb scents. Figure 5 shows how biopolymers can be used in the pharmaceutical sector.

Food Industry

Constraints related to the length of time food can be stored and sold pose challenges for the food and retail

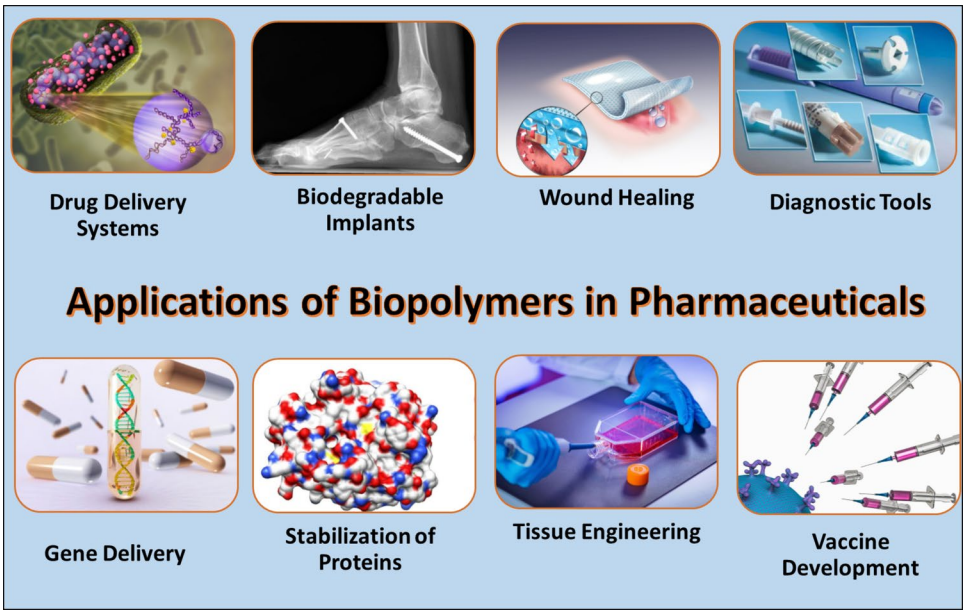


Fig. 5 Application of biopolymer in the domain of pharmaceuticals

industries. Various factors, including bacterial invasion, fungal infection, temperature changes, handling and storage techniques, and processing procedures, impact the deterioration of food after harvesting. Canned food, refrigerated systems, plastic containers, and other such methods are only a few of the many strategies used to lessen the impact of environmental factors that contribute to food spoilage. Such methods are commonly associated with concerns about environmental damage, food insecurity, lack of biodegradability, and power consumption [245]. Since biopolymers can encapsulate and release bioactive substances, prevent microbiological contamination, allow for gas diffusion, keep temperatures low, have nontoxic properties, and improve food safety, their use in food preservation and storage shows great promise [246]. Food packaging is the technique of sealing food to prevent decomposition due to exposure to the elements or contamination. Packaging plays a vital role in the food industry as most food items are sold and distributed in packaged form. Manufacturers need to ensure that packaging is user-friendly and lightweight for easy transportation from the manufacturer to the final consumer. Aesthetically pleasing packaging is also important for achieving marketing goals [247]. The cost of packaging materials can be high, so it is vital for all stakeholders participating in the consumption and manufacturing of food to possess a complete grasp of the different packaging possibilities at their disposal. Merely serving as a receptacle for food, food packaging has evolved into an integral component in preserving the quality and freshness of food. Developers have created multiple features in food packaging to ensure safekeeping, and efficient packaging can potentially reduce food waste and maintain products at their peak quality for the intended storage duration.

However, there are concerns about the impact of food packaging on the environment and the safety of the food itself. Commonly used plastic containers provide difficulties in waste management and may have subpar biodegradability when used as packaging. It has also been noted that, when heated, certain varieties of polythene and plastic, among other packaging materials, might release harmful chemicals. This could endanger buyers [248]. Solution casting was utilized to produce PVA-starch-based active biocomposite films with sepiolite clay and coconut shell extract. The incorporation of coconut shell extract enhanced the antioxidant and mechanical strength of PVA-starch films. Hydrogen bond interactions inside the film matrix may account for the increased strength reported. As an antioxidant, coconut shell extract could be utilized in the food industry. Additionally, it was revealed that PVA starch films showed appropriate qualities for active packaging purposes [249]. Biopolymer uses in the food industry are shown in Fig. 6.

Automobile Sector

Automobiles that employ biopolymers have enhanced characteristics such as reduced weight, heightened fuel efficiency, and increased resilience against heat and external forces. This development has facilitated the production of automobiles within the mid-range price bracket. The vehicle business has experienced a decrease in pricing and an increase in demand due to advancements in composites and industrial-scale production methods [250]. There are several potential avenues via which the integration of biocomposites

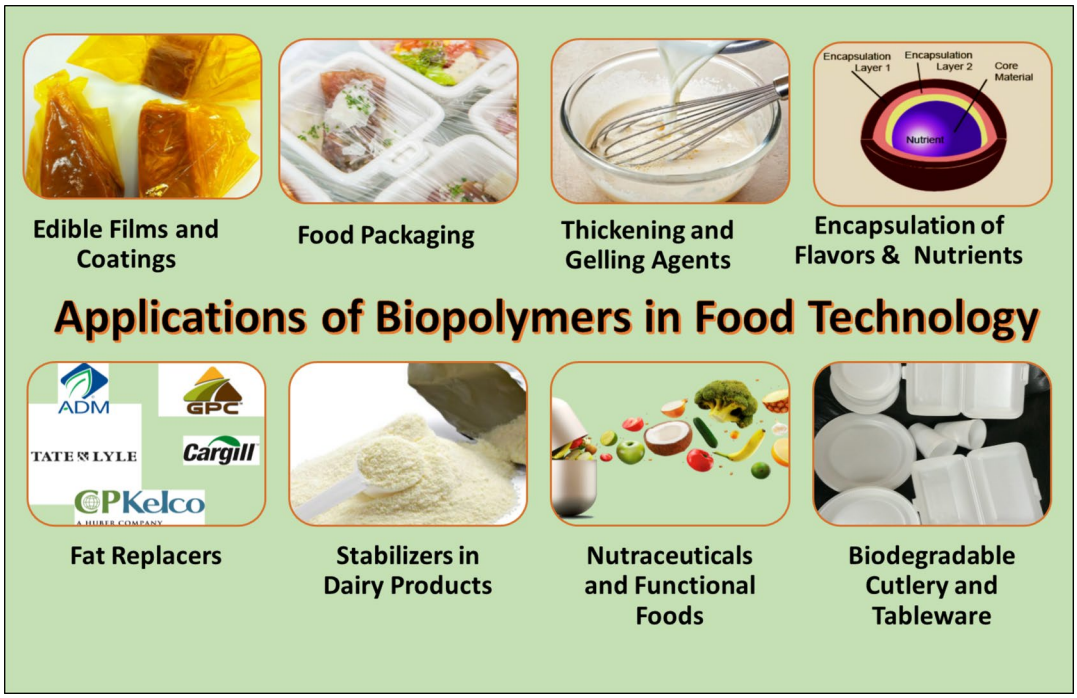


Fig. 6 Application of biopolymer in the domain of food technology

could enhance the automotive sector. Frequently, they exhibit reduced weight, resulting in decreased fuel consumption and diminished vehicular emissions. The thermal and acoustic properties of biocomposites are superior to those of non-renewable composites, rendering them highly suitable for utilization in vehicle interior components [251]. Biocomposites obtained from renewable resources, like agricultural waste, possess significant potential for application within the automobile sector, particularly in light of the escalating depletion of both environmental resources and petroleum reserves. Various non-structural interior parts, including seat cushions, interior panels, dashboards, wood trim, headliners, seat backs, and thermoacoustic insulation, might derive advantages from the distinctive array of properties offered by biocomposites. Currently, Audi utilizes flax/sisal natural fibers and polyurethane materials for the production of door trim panels. Additionally, specific automobile models from Audi employ cellulose-based biocomposites for the manufacturing of door panels, boot lid finish panels, and seatbacks [252]. Ford exemplifies the utilization of agricultural remnants in component manufacture through the production of a cabin storage bin composed of a blend of wheat straw and polypropylene. This practice not only contributes to the financial gains of farmers but also aids in the reduction of pollution [253]. In order to showcase the potential of lightweight and environmentally-friendly materials for load-bearing purposes, this automotive concept incorporates kenaf and hemp fiber reinforcements in conjunction with polyurethane foam. Although not all ideas materialize into marketable goods, they nonetheless serve as valuable tools for identifying patterns and forecasting future developments.

Construction and Household

As the global population passed the 8 billion marks in November 2022 and is projected to reach 9.7 billion by 2050 and exceed 10 billion by 2100, urbanization has risen around the globe. The increased demand for infrastructure and construction has prompted the construction industry to seek out sustainable building materials in order to satisfy population demands while preventing ecological crises and resource depletion [246]. . Materials made from natural fiber composites best serve the industry's eco-friendly mission. However, issues with longevity and fire resistance have reduced the use of biocomposites in construction. Wood is a natural composite that has several drawbacks as a building material, but humans have devised architectural and technical solutions to these problems, making wood one of the most important construction materials. Building materials, fixtures, fittings, and even household products like furniture could all benefit from the ongoing investigation into biocomposites for construction applications. The building sector makes extensive use of biocomposites for a wide variety of purposes, including insulation, sandwich panels, fillers, and reinforcement. Reinforcing concrete beams with kenaf fiber-reinforced polymer plates ultimately enhanced

their deflection, stiffness, and ultimate loading [254]. The flexural characteristics of concrete masonry walls, by using fiber fabric, improved the ductility and flexural capabilities [255]. They used a jute cloth mesh covering in the middle of the concrete beams to test their mechanical and physical qualities. They use an eco-friendly resin strengthened with hemp and linseed. While the linseed-reinforced composite showed better mechanical properties, the hemp-reinforced one was better at absorbing water and preventing fires [256]. Through the application of biocomposite as the external covering of structures, the researchers suggested the incorporation of numerous layers of polylactic acid (PLA) to mitigate flaws in the matrix and the resulting deterioration of the whole biocomposite laminate due to moisture and ultraviolet (UV) radiation exposure [257]. Extensive studies have been conducted to investigate the possibility of bio composites as environmentally friendly, high-performance construction materials and their application in the industry.

Market Trends and Commercialization Prospects

Based on industry analysis study and consultancy report focused on the worldwide polymer market, the anticipated value of this market in 2018 was an impressive $666.6 billion. Experts project substantial growth for the market, experiencing a growth rate of 5.1% per annum. Biopolymers significantly impact the global market of polymer as crucial organic molecules on a global scale. Specific industries determine the categorization of biopolymers based on their intended application. The market in question exhibits a wide range of end-users, encompassing several industries such as pharmaceuticals, healthcare, food, and beverages, among others. Biodegradable polyester holds significant utility within the medical field, particularly in the production of surgical implants. Biopolymers have significant applications in the food and beverage sector, particularly in the manufacturing of cellophane films, which are extensively used for food-packaging purposes. The global biopolymer market experienced substantial growth in 2018, with an estimated market value of $12 billion. It is anticipated that the biopolymer market will experience substantial growth at a compound annual growth rate (CAGR) of 19% over the period spanning from 2019 to 2025.

Biopolymers, formed from living organisms, are entirely biodegradable macromolecules. The most common types of biopolymers are lipids, proteins, nucleic acids, peptides, and carbohydrates. As a result of their origin in living organisms, these materials are carbon-neutral and may be easily recycled. Furthermore, biopolymers have the ability to capture and store the carbon dioxide that plants would otherwise release into the air. There are four groups of biopolymers: those based on sugar, synthetic materials, cellulosic materials, and natural polymers. Europe's massive 55.5% share of the global market in 2018 is evidence of the European Biomass Industry Association's various measures to increase the industry's use of biopolymers [245].

Real-world Examples of Regions Embracing Agro-food Waste Biopolymers to Attain Circular Economy

According to research by Colin Campbell, co-founder of the London-based Oil Depletion Analysis Center, only 746 billion barrels of oil remain in reserves after extracting 944 billion barrels throughout history. These statistics are disconcerting, as they suggest that a future devoid of oil may be within reach. In light of diminishing oil resources, it is imperative for companies to engage in innovation, investment, and invention in order to sustain their operations. The global biopolymer sector derives significant advantages from this phenomenon. The pharmaceutical sector widely utilizes biopolymers to address wounds of diverse magnitudes and intensities. Biopolymers including alginate, chitosan, gelatin, and pectin compose hydrogels that prevent desiccation in dry wounds [258, 259]. Furthermore, the field of wound healing utilizes these biopolymers as patches. These factors are expected to collectively drive the advancement of the biopolymer sector. The cost of initial manufacture holds significant importance in the biopolymer business. Several prominent participants in the market are collaborating with a farming company in an endeavor to discover a resolution that will stimulate the growth of biopolymers. ASF SE, Danimer Scientific, Novamont SpA, Galatea Bio Tech, Total Corbion, Plantic Technologies Ltd., FMC BioPolymer AS, Nature Works LLC, Sigma-Aldrich, and Biome Technologies Ltd. are prominent companies operating within the biopolymer market. Sigma-Aldrich is a chemical and polymer manufacturing company headquartered in the state of Missouri. They have been accountable for the synthesis of a diverse range of biopolymers and naturally occurring compounds, encompassing adhesive starches, proteins, cellulose, gelatin, chitosan, lignin, dextran, collagen, and polyamino acids [245].

Thailand

Thailand uses first-generation waste valorization methods to use leftover food for bioenergy and animal feed. Ruminant diets in Thailand include corn stover, rice straw, cassava chip, and sugarcane bagasse. Thailand has plenty of reserves to feed plants, making biogas production possible [260]. From 39.75 tons/day to 1987.50 m3/day, slaughterhouse waste biogas systems produce biogas. Thailand built 21 bioethanol facilities in 2016, generating 1.3 billion liters of ethanol annually at 81% capacity. Biorefineries prefer agro-food waste because it is less modified [160, 260]. The

Thai Energy Policy and Planning Office (EPPO) manages "A.T. Biopower" from agricultural waste to energy.

India

After competing applications including animal bedding, calf feed, organic fertilizer, heating, and cooking fuel, 34% of gross food residue in India is surplus trash. Dietary modulation of gut microbiota is becoming more popular for health promotion. Some research group found that *Aspergillus awamori* GHRTS produced fructosyltransferase from wheat bran, rice bran, and corncob [261]. Other oligosaccharides include xylo-oligosaccharides (XOS), which have been studied using wheat bran and Bengal gram husk [262]. A recent study compared orange and mango peels for lactic acid production. Mango peel has more cellulose, phenolic, and reducing sugars than orange peel (40% more lactic acid concentration). Banana residue as polymer reinforcement improved water resistance and thermostability [160]. India and the Europe have also committed to a joint initiative called "New Advances in the Integrated Management of Food Processing Waste in India and Europe" (NAMASTE-EU). Mango, pomegranate, and rice bran byproducts were promoted for India. Advanced technologies were used to convert products into novel foods and feeds for market spread. Interactive global projects generate knowledge and expand markets using mutual benefits and collaboration [160].

Hong Kong

Based on Hong Kong's massive food waste, numerous experiments have focused on valorizing unconsumed bakery products to value products in conjunction with Starbucks Hong Kong. The project began with the enzymatic hydrolysis of bread waste to produce bioplastic PHB and platform chemicals like succinic acid (SA). Following fungal solid-state fermentation, carbohydrates are broken down. *Actinobacillus succinogenes* and *Halomonas boliviensis* bioprocess bakery waste from a Starbucks in Shatin New Town Plaza to produce SA and PHB [57].

Chemical conversion of waste raw materials into bio-based products like biodiesel could increase valorization applications. The developed solid acid catalyst converted waste cooking oil with high free fatty acid (FFA) concentration to biodiesel-like biofuels. This solid acid catalyst could also esterify FFA and transesterify other triglycerides in waste oil. With the proposed solid acid catalyst, 98% methyl esters were produced without oil purification. This invention demonstrated the combined valorization of corncobs and waste cooking oils into a relatively pure biodiesel-like biofuel utilizing an environmentally benign and affordable solid acid catalyst. The Hong Kong Government can use such cooperative solutions to reduce food waste and develop eco-friendly platform chemicals, biopolymers, and biodegradable plastics [261, 263].

Challenges and Future Directions

In contemporary society, plastic and synthetic polymers have become ubiquitous, finding application across diverse sectors ranging from industrial settings to residential and commercial environments, despite their well-documented adverse ecological implications. The dilemma is rooted in the extensive ubiquity of plastic garbage, which exerts a significant influence on the environment across diverse ecosystems, ranging from towering mountains to the depths of the oceans. In order to tackle this issue, biopolymers have emerged as a viable and environmentally friendly option, leading to significant advancements in several industries such as medical devices and food packaging. Biopolymers present several advantages over synthetic polymers, including time and energy efficiency, user-friendliness, biodegradability, and cost-effectiveness. Moreover, they offer an environmentally responsible substitute for petroleum-based polymers. Despite the presence of certain obstacles, such as the issue of manufacturing costs and the need for enhanced durability, modern biopolymers have successfully surmounted these issues, thereby enabling their use in diverse domains such as food packaging, cutlery, and various plastic products. Consequently, their adoption has made a significant contribution towards promoting environmental sustainability. Advanced polymers possessing antibacterial and biodegradable characteristics are synthesized via techniques such as the fermentation of sugar beet and corn wastes. These polymers exhibit desirable attributes such as thermal processability and a low melting point. The incorporation of various polymers in a blend has been found to improve stress resistance and adhesion properties. Additionally, the inclusion of nanofillers in composite polymers has been observed to alter the surface area and aspect ratio of the resulting material.

Biopolymers are utilized in several fields such as drug delivery, tissue engineering, ceramics, and packaging materials, thereby facilitating the advancement of porosity scaffolds, artificial joints, and biofilms. Synthetic polymer-ceramic composites are of significant importance in the field of biomedical applications, particularly in the development of prosthetic bones and the treatment of bone disorders.The combination of biobased polymers and natural fibers results in the development of hybrid nano-composites that exhibit enhanced durability [264]. The incorporation of essential oils into biodegradable films has been found to augment its mechanical strength, moldability, and antibacterial properties. Biodegradable substances, such as banana and spinach,

are employed in water filtration systems to achieve dual purification and enhance nutrient content, thereby making a significant contribution to human well-being.

Biopolymers have the potential to function as substitutes for metals in the automotive industry, as they can be utilized in the form of lightweight tailored plastics. This application of biopolymers contributes to the reduction of vehicle weight, hence improving fuel efficiency. The market is witnessing a noticeable increase in the demand for biopolymers, and it is anticipated that advancements in this field will make a substantial contribution to the global economy.

Conclusion

In order to mitigate the issue of food loss and waste across the whole supply chain, it is imperative to adopt strategies aimed at minimizing waste generation and repurposing discarded materials into valuable goods. There are now multiple techniques available for the extraction of bioactives and biopolymers from food waste. However, there is a need for the development of novel technologies that can enhance the efficiency of extraction processes while requiring little investment. By accelerating the decrease of resource and energy consumption in food processing, these advancements can contribute to sustainable practices in the industry. The promotion of bioactives and biopolymers derived from food waste has the potential to reduce expenses associated with fortified foods and enhance their appeal. In order to optimize future valorization procedures, it is imperative to emphasize both economic feasibility and minimal environmental impact. Various protocols, such as anaerobic digestion, refined chemical separation, unified bio-conversion for biofuels, and advanced extraction technologies, exhibit considerable potential in terms of both environmental sustainability and economic advantages. However, the development of truly innovative techniques necessitates interdisciplinary collaboration among scientific fields. In order to properly adopt these advanced methodologies, it is imperative to establish a robust partnership among the scientific community, industry, and government. Efforts should be made across all sectors, encompassing food production and consumption, to mitigate the issue of food waste. Regulatory entities are responsible for ensuring that industry use innovative technologies aimed at mitigating food waste, while also educating customers about the significance of utilizing value-added goods resulting from such waste.

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Data Availability The authors confirm that the data supporting the findings of this study are available within the article.

Declarations

Competing Interests The authors have no relevant financial or non-financial interests to disclose.

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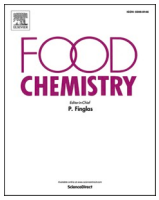

Review

Recent advances in artificial intelligence towards the sustainable future of agri-food industry

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ABSTRACT

Artificial intelligence has the potential to alter the agricultural and food processing industries, with significant ramifications for sustainability and global food security. The integration of artificial intelligence in agriculture has witnessed a significant uptick in recent years. Therefore, comprehensive understanding of these techniques is needed to broaden its application in agri-food supply chain. In this review, we explored cutting-edge artificial intelligence methodologies with a focus on machine learning, neural networks, and deep learning. The application of artificial intelligence in agri-food industry and their quality assurance throughout the production process is thoroughly discussed with an emphasis on the current scientific knowledge and future perspective. Artificial intelligence has played a significant role in transforming agri-food systems by enhancing efficiency, sustainability, and productivity. Many food industries are implementing the artificial intelligence in modelling, prediction, control tool, sensory evaluation, quality control, and tackling complicated challenges in food processing. Similarly, artificial intelligence applied in agriculture to improve the entire farming process, such as crop yield optimization, use of herbicides, weeds identification, and harvesting of fruits. In summary, the integration of artificial intelligence in agri-food systems offers the potential to address key challenges in agriculture, enhance sustainability, and contribute to global food security.

Abbreviations: AI, Artificial intelligence; ML, Machine learning; NLP, Natural language processing; ANN, Artificial neural network; MLP, Multilayer perception; DL, Deep learning; CNN, Convolutional neural network; DNN, Deep neural network; FL, Fuzzy logic; OLS-R, Ordinary least square regression; SL-R, Stepwise linear regression; RF-R, Random forest regression; SVM, Support vector Machine; kNN-R, k-nearest neighbours' regression; PC-R, Principal component regression; PLS-R, Partial least square regression; BLR, Boosted logistic regression; LSTM, Long-short-term memory; GA, Genetic algorithm; CSA, Colorimetric sensor array; TMA, Trimethylamine; MLR, Multiple linear regression; RBM, Radial Basis Model; TDNN, Time-delayed neural networks; BBO, Biogeography-based optimization; DC, Digital camera; PCA, Principal component analysis; FNNs, Feed-forward neural networks; FCSs, Fruit classification systems; SCV, Stratified cross validation; DCGANs, Deep convolution generative adversarial networks; PLS, Partial least square; IOTs, Internet of Things; DSIFT, Dense scale invariant feature transform; UAS, Unmanned aircraft systems; UAVs, Unmanned aerial vehicles.

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1. Introduction

Artificial intelligence (AI) is the replication of human intelligence by a system or machine. The goal of AI is to create a machine that can think like a human and emulate human behaviours such as perception, reasoning, learning, planning, and prediction. Intelligence is one of the primary attributes that distinguish humans from animals. With the inexorable occurrence of industrial revolutions, an increasing number of machine types continue to replace human labour in all sectors of life, and the approaching replacement of human resources by machine intelligence is the next major problem to be met. Many scientists are concentrating on AI, making AI research-rich and diversified. AI study areas include search algorithms, knowledge graphs, natural language processing, expert systems, evolution algorithms, machine learning (ML), deep learning (DL), and others. It is commonly recognized that food is an essential component of human survival and is the product of farming, produced after farmers distribute the many commodities they have created. Products from the food sector are essential for any nation's development (Kakani, Nguyen, Kumar, Kim, & Pasupuleti, 2020). It played with a huge part in the national economy and the global economy in the developing nation. Therefore, it is crucial to ensure the safety of food sector products and their high quality through appropriate distribution. AI is a recently developed technology that has produced positive results in achieving the required objectives in recent decades. Investigating the application of AI for smart agriculture and food businesses is an important aspect. Such methods deliver high-quality goods on schedule and satisfy social requirements. The food processing sector can create a lot of food products quickly with this current technology, which will exponentially boost the company's economy (Misra et al., 2020). AI-based systems are widely used in almost every aspect of technology. It enables the efficient transformation of food industry products, computerization of the food sector, and optimization of challenges. By utilizing a computerized system, the industry may review and assure that optimal conditions, such as seed picking, monitoring of crops, irrigation, and monitoring of temperatures, can be improved, resulting in the perfection of in agricultural sector with ultimately affect the food processing sector (Donepudi, 2014). Additionally, it is useful for processing of food, food storage, and food delivery. Robotics and intelligent drones are two examples of intelligent devices that can significantly and critically contribute to reducing the cost of packaging. It will also assist in transporting the food products, finishing the operation in hazardous conditions, and providing extremely high-quality goods (Bera, 2021). Management of food security and quality are the two major categories into which the significant responsibilities of AI in the food industry may be divided.

Therefore, in this review, we explored cutting-edge AI methodologies, such as ML, neural networks, and deep learning. Moreover, the application of AI in the agri-food industry, highlighting its role in ensuring quality across the production process is thoroughly discussed by placing a strong emphasis on both existing scientific insights and future research & development.

2. Artificial intelligence: State-of-the-art techniques

DL and ML are two of the most widely used AI techniques. Individuals, businesses, and governmental entities utilize these data-driven models to make predictions. Currently, machine learning techniques are being developed to address the complexity and unpredictability of information in the food business (Negi & Rajesh, 2019). Artificial Neural Networks (ANNs), Robotics, Expert Systems, Computer Vision, Natural Language Processing, and ML are the main subfields of AI. The natural language processing (NLP) is used to comprehend spoken people's language, computer vision to view analog-to-digital conversions like speech recognition, video, and expert systems to imitate judgment. Learning, which involves the acquisition of data and then creating algorithms to turn it into useful information; reasoning; and self-correction, are the three cognitive abilities that serve as the foundation for AI encoding. Recently, AI technology has made it possible to use it in the agro-food industry. AI has contributed to agro-food sector and supply chain and actually makes substantial contribution and assistance in comprehending identification of models, service generation, and in the process of decision-making. The AI has added a vital role in agriculture by delivering precise and predictive decision-making in order to increase productivity with retention of resource requirements (Patel, Rai, Das, & Singh, 2021). AI tools recommend algorithms to compute performance, classify patterns, and predict unexpected problems in order to solve agriculture comprehension problems, identify pests and the best treatments, and manage irrigation and water consumption systems with smart irrigation systems. Remote sensing and sensors are used to evaluate biotic and abiotic elements in order to improve agricultural and live-stock management (Patel et al., 2021).

The process of acquiring data from real-world sources, including as sensors, old documents, and client feedback, is known as data acquisition. Following that, the data is cleaned, normalized, and prepared as part of the data pre-processing process to guarantee consistency and quality. The third step entails integrating engineering with the data extraction of pertinent elements to feed the AI model that predicts the quality of the output. Subsequently, pre-processed data is used for model training in order to accurately anticipate product quality. The process as a whole, including data annotation, model validation, interpretability, and ethical compliance, is assessed by human supervision that guarantee the AI model functions properly and complies with quality requirements and laws.

2.1. Machine learning

ML is a significant branch of AI that promotes the creation of more creative and productive labour. Fig. 1A shows the two categories and types of ML that are available for the applications and Fig. 1B represented several algorithms employed in food processing machine learning activities. The two main tasks in the ML technique are supervised learning, and unsupervised learning (Shetty et al., 2022). Supervised machine learning requires supervision, as the name implies. Using supervised learning and the "labelled" dataset, computers are trained, and following training, the computer generates predictions. In this case, the labelled data show that the inputs and outputs were correctly mapped. The creation of the map between input and output variables is the goal. Applications for supervised learning include risk assessment, spam filtering, and fraud detection. With unsupervised machine learning, the computer learns from an unlabelled dataset and makes its own predictions about the outcome (Li, Shepperd, Guo, & Technology, 2020). In this case, the dataset used to construct the models has not been tagged or classified, and they are then free to act on their own. Sorting the unsorted dataset into classes or groups according to similarities, patterns, and variations is the main objective of this learning process. The computers are supposed to find the hidden patterns in the input dataset.

In ML, mathematical and statistical techniques are applied to learn from datasets and make predictions and judgments based on the data. Two systems, the symbolic approaches and the sub-symbolic approaches, can be distinguished generally. The impact of this strategy, as per supervised learning, is to map the variables to the selected output variable (Traore, Kamsu-Foguem, & Tangara, 2017). Using the labelled data and knowledge about the desired input and output variables, a predictive model is built. There are several algorithms employed in supervised learning techniques, but decision trees, Bayesian networks, and regression analysis stand out. In actuality, and as Jordan & Mitchell mentioned (Jordan & Mitchell, 2015), using an unlabelled dataset, this unsupervised ML instance developed the hidden patterns and is mostly utilized for dimensionality reduction and exploratory data analysis. In this specific ML challenge, training and test datasets are combined while the learner interacts with the environment to collect data. To learn

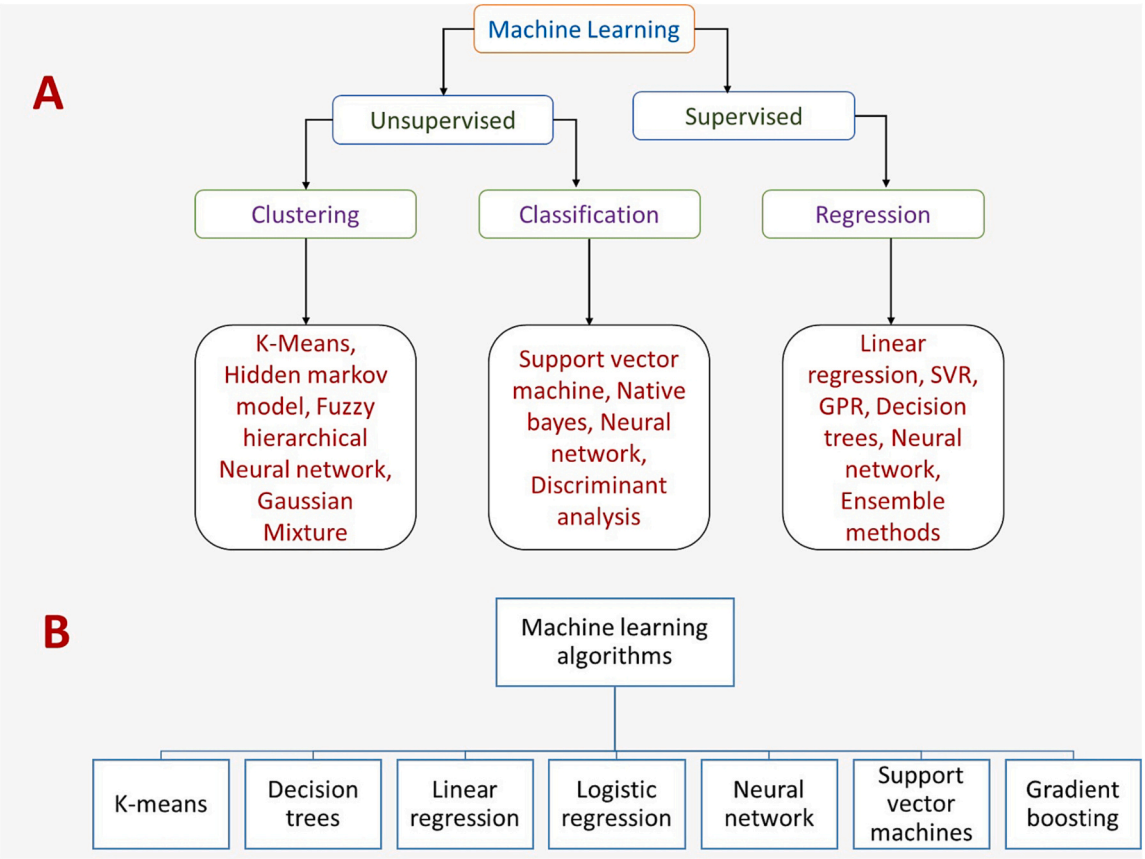

Fig. 1. (A) classification of machine learning and (B) machine learning interpretation in the food business using different algorithms.

more, the learner must experiment with novel, untested acts as opposed to employing the information already gained (Mohri, Rostamizadeh, & Talwalkar, 2018).

2.1.1. *Artificial neural network (ANN)*

An ANN is a further AI component and has higher possibilities for the use in food industry. In terms of unsupervised learning, it utilizes unlabelled datasets without sufficient information of output and input variables and uses methods like ANNs, clustering, genetic algorithms, and deep learning. ANNs is the mostly employed technique for determining the quality of food in AI applications. An ANN is a node-based mathematical model that can have either linear or non-linear processing features (Sun, Zhang, & Yang, 2019). Theoretically, an electric signal travels through synapses at the tips of each node of an interconnected neural network, passing through neurons with the assistance of axons (Jha, Doshi, Patel, & Shah, 2019). The human brain and ANN both operate on similar principles, alerting the system to perform an internal task rather than a traditional computational activity. The three primary layers that make-up the basic architecture of an ANN (Fig. 2A). The architecture includes activation mechanisms, including feed-forward or feedback mechanisms. In order to process the unprocessed data, the input layer connects to the hidden layer after obtaining the data from the architecture. To construct the final output, the collected data is then delivered to the output layer attached via the nodes. The ability to forecast the foundation of parallel reasoning and effectively train neural networks is one of the major advantages of ANN layers. An ANN works as a human brain and is capable of learning and accumulating synaptic weights, which are the connections between neurons. According to Sukhadia and Chaudhari (2019), the setup of ANN is developed in such a way that it may support specific applications, including pattern recognition or data classification (Sukhadia & Chaudhari, 2019). Also, Gonzalez-Fernandez et al. (2019) asserts that ANN is versatile, adaptive, and applicable to a variety of issues and circumstances (Gonzalez-Fernandez et al., 2019). They also noted that although modifications are required, ANN is flexible to different circumstances and may be used to simulate the majority of non-linear systems. Additionally, non-linear regression is one of ANN's most notable characteristics. The multilayer perceptron (MLP) is the most often used network for pattern recognition and prediction. The learnt internal representations of the input data are represented by the data in a neural network's hidden layer. Throughout the training process, the network's parameters—weights and biases—interact intricately to create these representations. The network's black-box nature makes it difficult to precisely interpret these representations, but methods like feature analysis, visualization, and trained weight interpretation can shed some light on the characteristics and patterns the hidden layer neurons are picking up from the input data.

2.1.2. *Deep learning*

Deep learning (DL) is one of the fields of AI in which adulteration and defect detection have recently achieved exponential development. The development of DL models started in the late 1990s with the invention of CNN. One of the most effective ways to learn the deep features of digital data input for tasks connected to classification and regression is through the use of CNN (J. Singh, Thakur, Ali, Gera, & Kwak, 2020). CNN networks vary from traditional neural networks which are employing with number of convolutional layers. Standard CNN architecture for analyzing and detecting food is illustrated in Fig. 2B. Convolutional layers are built using filters to extract features from input images. The padding, stride, kernel size and activation parameters that are used to create convolution layers are produced based on the job at hand and should be optimized accordingly. Completely connected layers were placed at the layer end that serves as the classifier and consists of a completely linked network block to produce the output. For the categorization of images related to food and agriculture, a number of CNN

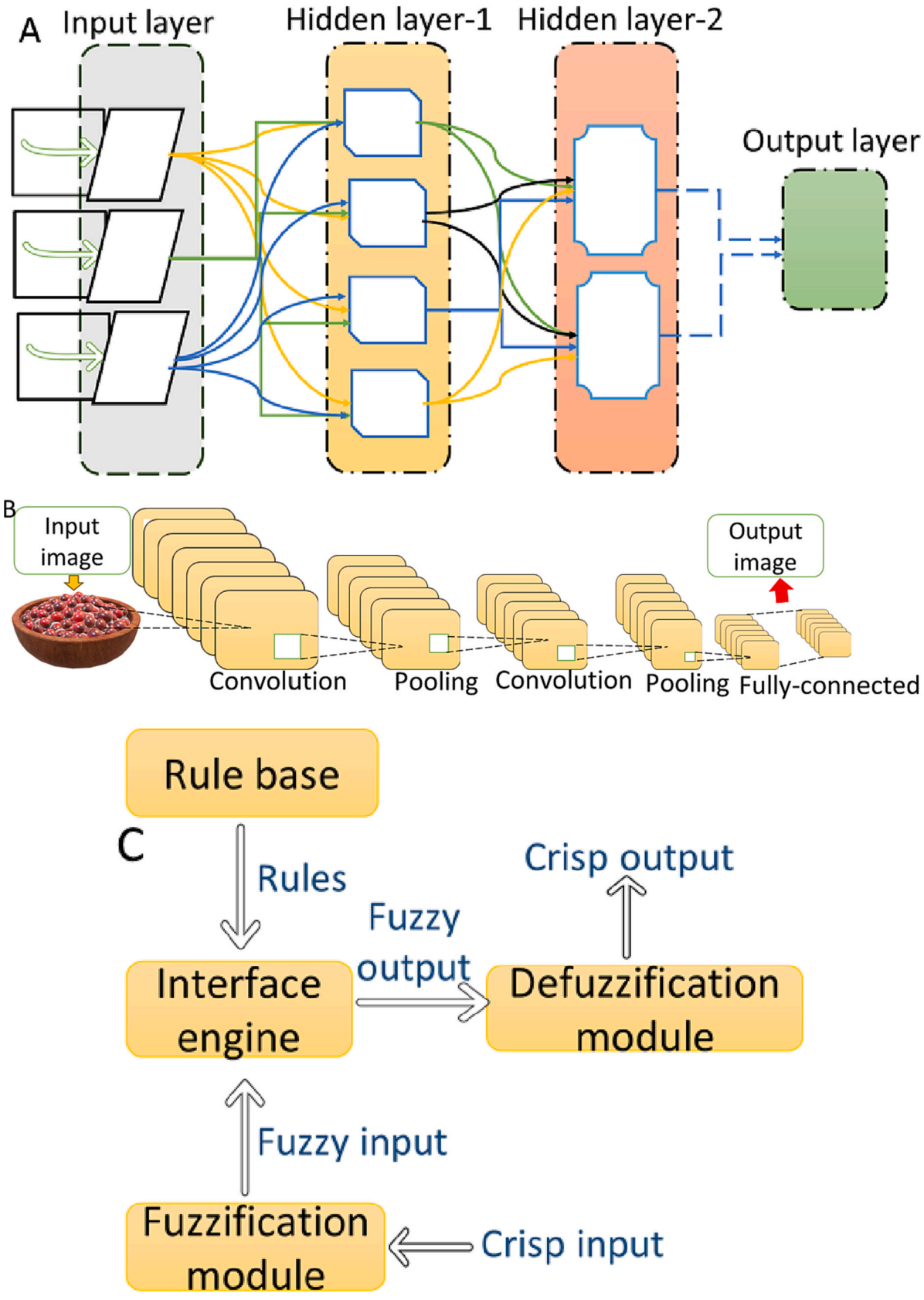

Fig. 2. Architecture of artificial intelligence technologies. (A) artificial neural network layers, (B) standard convolutional neural networkfor analyzing and detecting food, and (C) Fuzzy logic with four main parts.

architectures are currently available, including LeNEt, AlexNet, VGG, GoogLeNet, ResNet, and Inception. CNN is effective in detecting food adulteration and assessing the quality of agricultural items (Griffel, Delparte, Whitworth, Bodily, & Hartley, 2023).

2.1.3. Role of machine learning in food processing and preservations

ML algorithms can be applied in many different contexts to guarantee the safety of fruits and vegetables. For instance, supervised learning methods like support vector machines (SVMs) can be used to find possible toxins in food items. Fruits and vegetables that may have microbial contamination can also be found using SVMs (Kim et al., 2023). Grouping related food products together and identifying outliers that may be sources of contamination can be accomplished through the use of unsupervised learning techniques like k-means clustering. Unusual patterns that can raise questions about food safety can be found using anomaly detection techniques like isolation forests. Finally, an ideal inspection and reaction procedure to handle concerns about the safety of fruits and vegetables can be developed using reinforcement learning algorithms (Roy et al., 2023). Fruit preservation can benefit from ML in a number of ways. Algorithms for machine learning, for instance, can be used to track the quality of fruit that has been preserved and notify users when certain conditions are not met. In order to maximize fruit preservation, ML can also monitor and modify environmental factors like humidity and temperature. To guarantee that the fruit is fresh for the consumer, ML helps forecast the best times for fruit harvesting, packing, and distribution (Nile et al., 2020).

ML models can be used to estimate the remaining shelf-life of perishable food items depending on a range of factors, such as product features, initial quality, and storage conditions (Ulussever, Ertuğrul, Kılıç Depren, Kartal, & Depren, 2023). The program examines the deterioration patterns in the data to give accurate estimations of how long a given food will stay fresh and safe to eat. By applying this knowledge, one may reduce waste, enhance inventory control, and prevent consumers from purchasing defective items (Hu, Ahmed, & L'Abbé, 2023). Perishable food shelf-life can be estimated by ML algorithms based on a variety of parameters, including product attributes, starting quality, and storage circumstances. Through data analysis of deterioration trends, the computer generates accurate predictions about the shelf-life and safety of certain products. Making use of this data helps improve inventory control, cut down on waste, and stop consumers from buying faulty products (Torres-Sánchez, Martínez-Zafra, Castillejo, Guillamón-Frutos, & Artés-Hernández, 2020).

2.2. Expert system

A component of AI called an expert system brings expertise and the capacity to solve complicated issues utilizing reasoning and knowledge representation. The general form of an expert system, however, consists of an interpreter, an inference engine, a dynamic database, a human-machine interface, and knowledge acquisition. In this way, the expert system's problem-solving stage is used to imitate the way an expert think through knowledge and information. With the enhancement of a small group of variables and numerous factors based on prediction performance, an export system operating on common devices has been developed. By choosing features based on colour, texture, and geometric aspects, it was possible to estimate the fruit's ripeness with a classification accuracy of 100%. In order to recognize fruits, Duong, Nguyen, Di Sipio, and Di Ruscio (2020) developed an expert system employing the Efficient Net and MixNet deep neural network (DNN) architectures. Compared to a well-known baseline, both topologies successfully increased the total classification accuracy up to 95% (Duong et al., 2020). To assure their commercial usage for food and agricultural product quality inspection, it is required to establish the precise development of expert systems. Practically, the pace, monitoring procedure, and automatic detection are used to assess an expert system's performance. Since input functions are readily available, their implementation is required to define with their accuracy and speed of operation.

2.3. Fuzzy logic (FL)

The FL simulates how complicated judgments are made by people when given unclear and uncertain information. It is demonstrated to be a useful tool for handling classification issues involving imperfect data. Fuzzy, however, needs to work with better recovery, especially with added constraints while working with highly dimensional or massive volumes of data. Fuzzy systems enable the use of more simple algorithmic formulations and language variables to explain the behavior of a complex system instead of doing it quantitatively and mathematically. FL was crucial in the creation of the control systems for sophisticated processes used in the manufacture of food and beverages. The rule base, fuzzification inference engine, and defuzzification are the four essential components of a typical FL design, as depicted in Fig. 2C. According to the fuzzy set theory, an element is considered to be a member of a fuzzy set if and only if it has a real number in the range [0,1] (Hannan et al., 2019). The FL models involves different steps, including fuzzifcation, inference systems, and defuzzification processes (Wu et al., 2024). Fuzzifcation is a method that produces fuzzy input sets by converting a crisp value into a degree of membership. The membership functions' equivalent degree typically ranges from 0 to 1 (Alsaqour et al., 2015). The most popular membership functions are triangular, *Z*-shaped, S-shaped, trapezoidal, and Gaussian-shaped, while there are many others available (Alsaqour et al., 2015). The position called inference system where fuzzy rules are used to translate the fuzzy input into output. The final stage of the fuzzy logic model called defuzzification (Abd Ali, Hannan, Mohamed, & Abdolrasol, 2016). Mean of maximum, centre of maximum, centre of gravity, centroid of area, smallest of maximum, and largest of maximum are some of the different defuzzification techniques. Similarly, Kanade et al. (2018) evaluated the use of FL and the e-nose sensor to categorize guava according to ripeness levels (Kanade et al., 2018). The FL module's results produced classification accuracy for guava fruit ripeness estimation of 90%. Similarly, Villaseñor-Aguilar et al. (2020) used the FL method for the total soluble solids prediction, and the bell pepper maturity phases were found (Villaseñor-Aguilar et al., 2020). The classification of four bell pepper maturity stages using FL models yielded a precision of 88%. Another study by Pakyürek et al. (2019) utilized the FL method to grade the quality of three different types of pineapple (Pakyürek et al., 2019). FL has shown that it performs well as a control system, particularly when concerning with complicated processes for determining food and agricultural products quality.

2.4. Computer vision system (CVS)

According to Lukinac, Jukić, Mastanjević, and Lučan (2018), it involves a number of processes, including image processing, digitalization, analysis, and captures using the use of the visible spectrum falling on a surface of a reflective, absorbent material, images are obtained using the image analysis method. Photons are then caught by camera lenses and converted into electrical signals by an image sensor. Digitization is the process of converting these images into a numerical format (Lukinac et al., 2018). They reported that CVS can measure the external characteristics that form digital images to maintain control over the quality of the product through automated examination.

As AI continues to evolve rapidly, incorporating advancements in machine learning, expert systems, fuzzy logic, and computer vision, it offers unprecedented opportunities for innovation and impact across various domains. However, when tackling complex or multidimensional production/consumption networks, the optimization of AI models is needed to enhance efficiency, adaptability, and resilience. AI models should be optimized to streamline operations by minimizing resource wastage, reducing production costs, and improving overall productivity. Moreover, resource allocation becomes a crucial focus, with optimization algorithms ensuring effective distribution across various nodes to

meet demand while minimizing shortages or excesses. Additionally, AI-driven supply chain management aims to forecast demand accurately, optimize inventory levels, and identify potential disruptions to maintain seamless operations.

On the other hand, risk mitigation strategies are integrated, leveraging AI to identify and address risks, such as supply chain disruptions or market fluctuations. Ultimately, the adaptability and resilience of AI models are emphasized, continuously learning and adjusting to changing conditions to maintain performance and mitigate disruptions within complicated production/consumption networks. Through these optimization efforts, AI models contribute to enhancing the efficiency, agility, and reliability of these intricate networks.

3. Applications of AI in food industry

The AI approach offers a lot of benefits, and the food sector has been implementing it for decades with following growing trends in recent time. The AI can be use in the place for the traditional food productions system. This can be done by creating new AI models or adapt current ones to the special requirements and difficulties associated with the production of meat, beverages, and cultured meat. This could entail developing models expressly designed to forecast quality metrics, enhance manufacturing process, or guarantee regulatory adherence in the food production industry (Kakani, Nguyen, Kumar, Kim, Pasupuleti, and Research, F, 2020). In order to continuously learn from real-time data gathered during the creation of food items, implement feedback loops within AI systems. As it obtains more experience with the new technology, this allows the AI system to adjust and enhance its predictions and suggestions over time. However, the innovation of AI applications has been elevated in recent years towards the food processing sector by 2015. The utilization of ANN in a variety of activities in the food processing sector. Based on the R^2 values, all applications have performed satisfactorily, demonstrating that ANN is capable of producing results that are precise and dependable. Ordinary least square regression (OLS-R), stepwise linear regression (SL-R), random forest regression (RF-R), support vector Machine (SVM) regression, k-nearest neighbours' regression (kNN-R), principal component regression (PC-R), partial least square regression (PLS-R), and boosted logistic regression (BLR) are some of the ML techniques used in the food industry. Studies revealed that the application of ML has assisted in decision-making, lowering the cost of sensory evaluation, and improving corporate strategies to meet user needs (Lyu et al., 2020). The food processing sector used long short-term memory (LSTM), a synthetic recurrent neural network, for pH sensing during cheese fermentation (Kráľová & Jampílek, 2021). Similarly, the genetic algorithm (GA) was useful in predicting the fouling rate in food processing and was also used to define the food parameters (D. Kim, Zohdi, & Singh, 2020). Furthermore, ML was able to forecast the food waste quantity and also provided knowledge on the production process.

For monitoring of freshness in beef, a novel colorimetric sensor array (CSA) made of oxidized chitin nanocrystals (O-Ch-NCs) paired with a CNN was created (Jia, Ma, Tarwa, Mao, & Wang, 2023). CSA was treated to methylamine (MA), trimethylamine (TMA), and ammonia (NH_3) at concentrations ranging from 10 to 100 ppm. The discoloration was noticeable, as seen in Fig. 3A, notably for the bromocresol green. At 70 and 100 ppm concentrations, it shifted from yellow to blue for all the three gases. However, nuances may be indistinguishable to the human eye, especially when the concentration of volatile gas was lower, as it was at the earliest stage of decay. The data analysis was done using PCA and HCA methods to assess the CSA sensitivity to various gases in order to estimate the limit of detection. Two principal components were used to generate the PCA plot, demonstrating that three amine gases clusters which were clearly separated (Fig. 3B). When compared to the original, NH_3 and TMA were clearly recognizable, although MA at low quantities was indistinct. It is also worth noting that two eigenvectors only accounted for 87.19% of the total variance, but five eigenvectors might

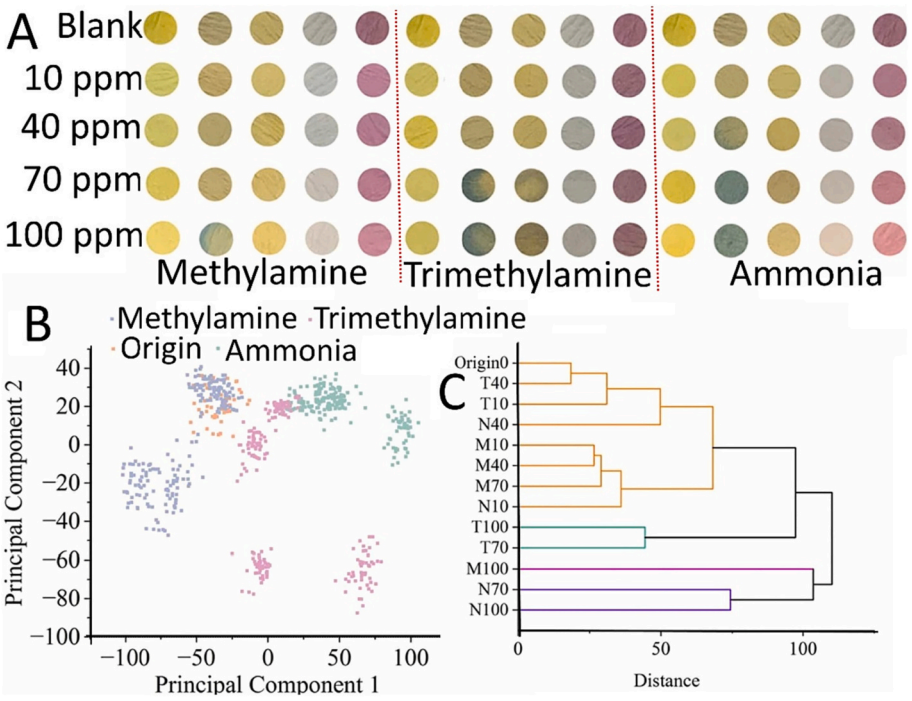

Fig. 3. Colorimetric sensor array for qualitative and quantitative analysis of methylamine, trimethylamine, and ammonia. (A) colour change for the sensor arrays exposed to different concentrations of methylamine, trimethylamine, and ammonia, (B) principal component analysis classification plot, and (C) Hierarchy cluster analysis dendrogram. In Fig. 3A, colourings are curcumin, bromocresol green, bromocresol purple, zinc tetraphenyl porphyrin, methyl red, considering from left to right, while T, M, and N in Fig. 3C represents methylamine, trimethylamine, and ammonia, respectively at different concentrations in ppm. Panels A-C are reproduced with permission (copyright © 2023 Elsevier B.V., Amsterdam, the Netherlands) from Jia et al. (2023). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

account for 95% and seven eigenvectors could account for 99%. This suggested that the inter-section phenomena were unavoidable in order to meet real applications and that at least three distinct dyes were required to achieve up to 99% accuracy. Many prior reports confirmed this result (Wang et al., 2022). In addition to PCA, the HCA dendrogram revealed with formation of three amine gases with different independently formed clusters at higher than 70 ppm (Fig. 3C). At 70 ppm for NH_3 and TMA, and 100 ppm for MA, the colour shift of CSA deviated significantly from the starting colour. Wang, Cheng, et al. (2022) reported over creations of colorimetric strip sensor array with bromophenol blue (BPB) and BCG and evaluated colour variations in NH_3. At 150 ppm of NH_3, their data revealed a substantial colour changes from yellow-green to blue-green (Wang et al., 2022). The CSA sensitively operated in comparisons to others, and both PCA and HCA results strongly supported the usefulness of CSA in identifying MA, TMA, and NH_3 as per combined cross-reactive interaction. The shape, size, and colour changes during storage, shelf-life prediction, browning, and melting qualities are examples of external quality attributes. In most cases, equipment, professional inspectors, or food inspectors themselves will analyze the quality of the food. For external quality inspection of products, there are various varieties of Computer Vision Systems (CVS) available, including hyperspectral, multispectral, and standard CVS (Lakshmi et al., 2017). We can forecast the faults in grains based on their size and form by using image analysis. Defective beans are simpler to remove while maintaining product quality (Pizzaia, Salcides, de Almeida, Contarato, & de Almeida, 2018). An electronic nose is a technological advancement in the study of smell. It operates on the basis of the mammalian olfactory system and uses gas sensors, which are also employed in the wine and coffee industries (R. B. Roy, Tudu, Bandyopadhyay, & Bhattacharyya, 2019).

To ensure product quality, the food and beverage sectors use e-noses. According to the guidelines established by the Speciality Coffee Association of America (SCAA) Technical Standards Committee, the effectiveness of roasted coffee is determined by the coffee cupping method (Thazin, Pobkrut, & Kerdcharoen, 2018). After being ground into a powder for five grams of coffee, the beans were boiled for three to five minutes at a temperature of 97 °C (Lingle & Menon, 2017). The radial basis function ANN is used to forecast the cupping method, which is used to collect the data. The computer analyses signals from the gas sensors in the e-nose using the Lab VIEW software. Multivariate data analysis is used to analyzed e-nose data (Thazin et al., 2018). The three sections of this experiment are as follows: the first examines the impact of temperature (10 °C to 90 °C) on liquid coffees' scent characteristics; the second classifies the acidity levels of different roast levels for coffee. Finally, humans test the levels of bitterness and provide instructions using a radial-based ANN (Thazin et al., 2018). Like the e-nose, the e-tongue is also used to assess the quality of various drinks, including milk, coffee, tea, wine, and beer. This e-tongue can detect the following parameters: bitterness, sourness, and salinity (Tan & Xu, 2020).

3.1. Dairy industry

The longevity of process cheese is predicted using two different ANN models: the multiple linear regression (MLR) model and the Radial Basis Model (RBM) with Fewer Neutrons (Goyal & Kumar Goyal, 2012). Based on R^2 values, they found that the RBM performs marginally superior than the MLR model. They also came to the conclusion that the MLR model works better for coffee drinks. To keep the raw milk from spoiling, fuzzy logic is used in storage. The spoilage of raw milk can be prevented by taking the following three steps: (I) Fuzzy inferences are used to predict temperature from the lining times; (II) The temperature data was handled in a fuzzy manner; (III) Warn the dairy farm employees. FL and the BP neural network are used to prevent milk from deteriorating. These technologies are enhanced by IOT, which increases the accuracy of the detection process. An alternative neural network that forecasts cheese shelf life uses time-delayed neural networks (TDNN), which operate on continuous input data. Two layers make up the TDNN: single and multilayer models that forecast how long food products will last on the market (Negash, Vasant, & Jufar, 2018). Similar to this, milk also contains additional nutrients like lipids and proteins in addition to lactose, which is the main carbohydrate. Manufacturers are removing extra lactose from milk to make it easier for consumers to digest or eat small amounts of lactose in order to avoid the issues brought on by lactose, such as lactose intolerance (Pawłowska, Umławska, & Iwańczak, 2016). Lactose is removed using an adsorption technique that uses fixed bed columns and empirical models from ANN (Balieiro et al., 2016). The adsorbent gets constantly associated with solution using these approaches; the adsorption rates are also increased. By the usage of common substances within the automated extraction of stable-level engraved silica in a set-mattress phase, molecular imprinting can enhance the adsorbent efficiency (Oliveira, Santos, Lima, Soares, & Leite, 2015).

To keep raw milk from spoiling, FL is used during storage. The first of (i) Three actions to prevent raw milk from spoiling is to predict temperature using fuzzy inferences based on lining times, (ii) The temperature data was handled in a fuzzy manner, and (iii) Give the dairy farm labourers a scare. Milk degradation can be prevented with the aid of FL and BP neural network. The inclusion of IOT in these technologies enhances the accuracy of the detection approach (Ma, Fan, Li, & Tang, 2018).

ANN has been developed to estimate the shelf life of processed cheese held at 30 °C. It can also measure the high protein content of ripped cheddar cheese, which can be utilized as an additional source of protein to beef. This is a tactic that combines a number of ingredients, including emulsifier, salt, water, and some specific spices. The mixture is continuously mixed while being heated in a jacketed vessel to achieve a uniform mass. Another neural network called time delay neural network (TDNN) uses continuous input data to forecast the shelf-life of cheese. The two layers that make up TDNN are single and multilayer models that forecast the food products' shelf lives (Negash et al., 2018). Similarly, lactose from the milk is removed by an adsorption method that uses empirical models created by ANN and is carried out using a fixed bed column (Balieiro et al., 2016). Because the adsorbent is in constant contact with the solution using these approaches, the adsorption rates also rise (Leite et al., 2019).

Lactose content is measured using High Performance Liquid Chromatography (HPLC) following the absorption process. The Radial Basis Function (RBF) model offers excellent efficiency, speed, and simplicity in addition to the MIP model. RBF needs more neurons in hidden layers than MIP, but it also needs more neurons in each layer for varied tasks. Researchers used MATLAB to build these two models, which are detailed in full by Leite et al. (2019). There is a detailed discussion of both MIP and RBF created neural structures; the accuracy of these structures' performance is verified by comparing them to other models (Leite et al., 2019).

3.2. Soft drink and beverage industry

Three categories of drinks are distinguished: (a) alcoholic beverages; (b) non-alcoholic beverages; and (c) hot beverages. There is no way to keep tabs on the fermentation process in a conventional brewery in real time, but with the help of AI and its digital tools, controlling and monitoring the brewing process can be achieved (Vassileva & Mileva, 2010). The use of AI techniques to regulate the brewing process, including CVS, FL, neural networks, and its hybrid intelligence methods. ANN assists in reporting the fermentation of beer (Vassileva & Mileva, 2010). In order to prevent weight gain or obesity, deep CNN assists in obtaining nutritional information about soft beverages. Using the bottle size and cap ratio, this method can estimate the nutritional content. It applies to other fruit-based beverages in addition to carbonated beverages. By removing the backdrop from the image as part of CNN's image processing process, nutritional content may be estimated (Hafiz, Haque,

Rakshit, & Uddin, 2022).

According to Ren et al. (2023) investigates the issue of the expensive and time consuming traditional R&D work in beverage demand diversification by building a model combining electronic sense and ML to anticipate the processes and formulas for vegetable-fruit beverages (Ren et al., 2023). The model's prediction performance was influenced following data pre-processing, as seen in Fig. 4. The R^2 of three models (kNN, RF, and DNN) increased to varied degrees following standardization when compared to models without scaled processing. The methods opted for standardization impacted on DNN, as indicated by R^2 values shifting from negative to positive value. Because of standardization, the DNNs called model was prominent in all models, and the DNN, scaled model was the best of all models. With an R^2 of 0.91, the DNNs called model effectively predicted formulas based on sensory information. The model performance in forecasting formulas was inadequate when based on e-nose, e-tongue, rheometer, and colorimeter data separately, as evidenced by the low R^2 value and large RMSE and MAE values in Fig. 4. When compared to the R^2 of models developed using individual e-nose, e-tongue, rheometer, and colorimeter values, the R^2 of models generated using fusion data were virtually all >0.60. The fusion data were crucial for constructing an accurate model with the right algorithm. In general, prediction performance based on fusion methods outperformed prediction performance based on *E*-nose or E-tongue sensing information (Hong & Wang, 2014). ML is commonly utilized in the regression problem of ingredient prediction and is developing as a useful tool in predicting specific components. However, it has yet to be used to predict complex formulas. ML was used in this work to forecast the formulations of beverages form sea buckthorn-passion fruit juice made with the same technique. On the testing set, the model's performance was estimated using RMSE, MAE, and R^2. A higher R^2 value and lower RMSE & MAE values imply superior model performance, resulting in higher beverage formula prediction accuracy (Fig. 4).

3.3. Fruit and vegetable processing industry

Using the AQS 602 machine, which sorts 3 to 5 tons of potatoes every hour (Nachev, Titova, & Damyanov, 2012),potatoes are supplied by a stream that is formed by belt conveyors, each of which requires specific attention and management (Fig. 5A). With the aid of a PMC photometric camera, these sorting systems sort the potatoes according to the formation of the tubers (Nachev et al., 2012). Fruit classification systems are useful for ranking various fruit varieties, but they are not ideal; for example; (I) not all classifiers are appropriate for all fruit varieties, (II) more sensors were needed, (III) fruit misclassification, (IV) fruit classification systems (FCSs) poor performance. An advanced computer vision-based FCS that uses a digital camera, additional enhancements for testing various fruit varieties, feed-forward neural networks (FNN), latest world optimization technique, and biogeography-based adaptive control to lower the rate of misclassification have been developed to improve these conditions (Yudong Zhang et al., 2016). With more precision and effectiveness, biogeography-based optimization (BBO) is employed in a variety of fields. The undesirable background is removed using a split merge technique. After digital camera (DC) fruit image collection, principal component analysis (PCA) is utilized to lower the size of the hybrid feature. The decreased images are then sent into FNN, which has the potential to categorize any nonlinear separable styles, after being removed from the chromatic fruit pictures. It only needs one

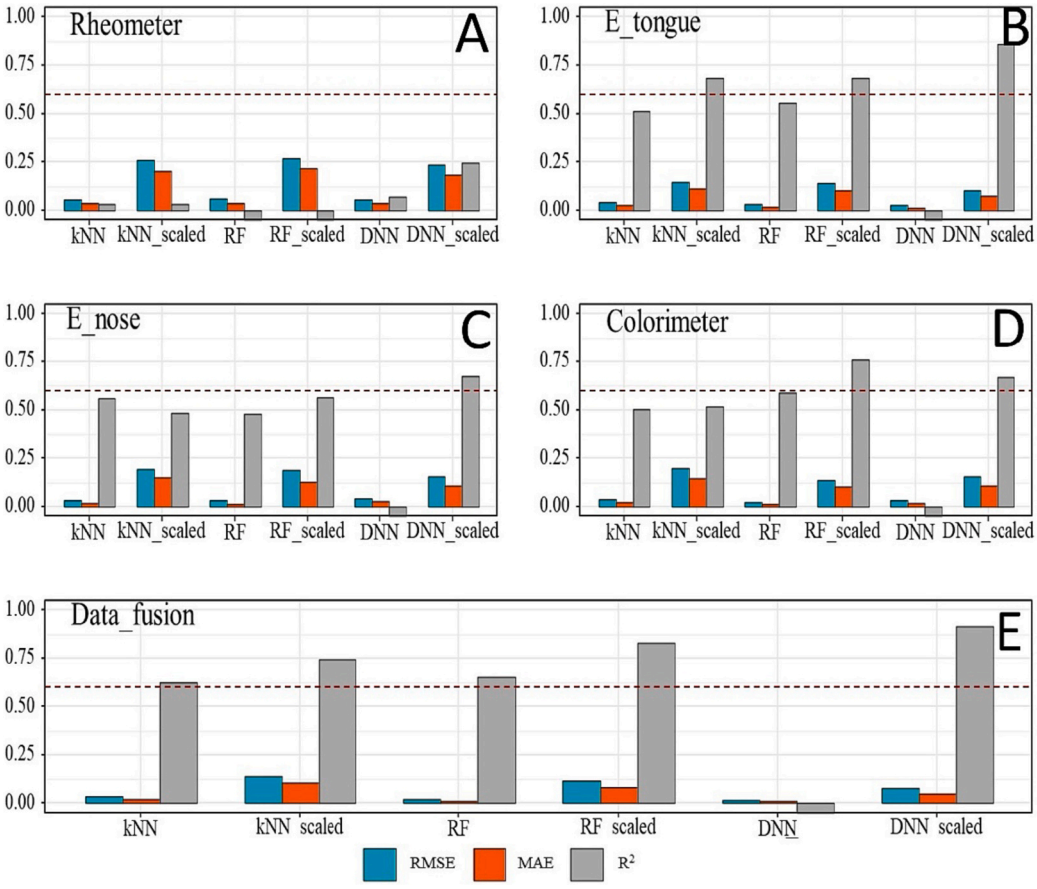

Fig. 4. Evaluation of electronic sense sensory prediction formula models for beverages. (A) Rheometer, (B) *E*-tongue, (C) E-nose, (D) Colorimeter, and (E) Fusion information of rheometer, E-tongue, E-nose, and colorimeter. This Figure is reproduced with permission (copyright © 2023 Elsevier B.V., Amsterdam, the Netherlands) from Ren et al. (2023).

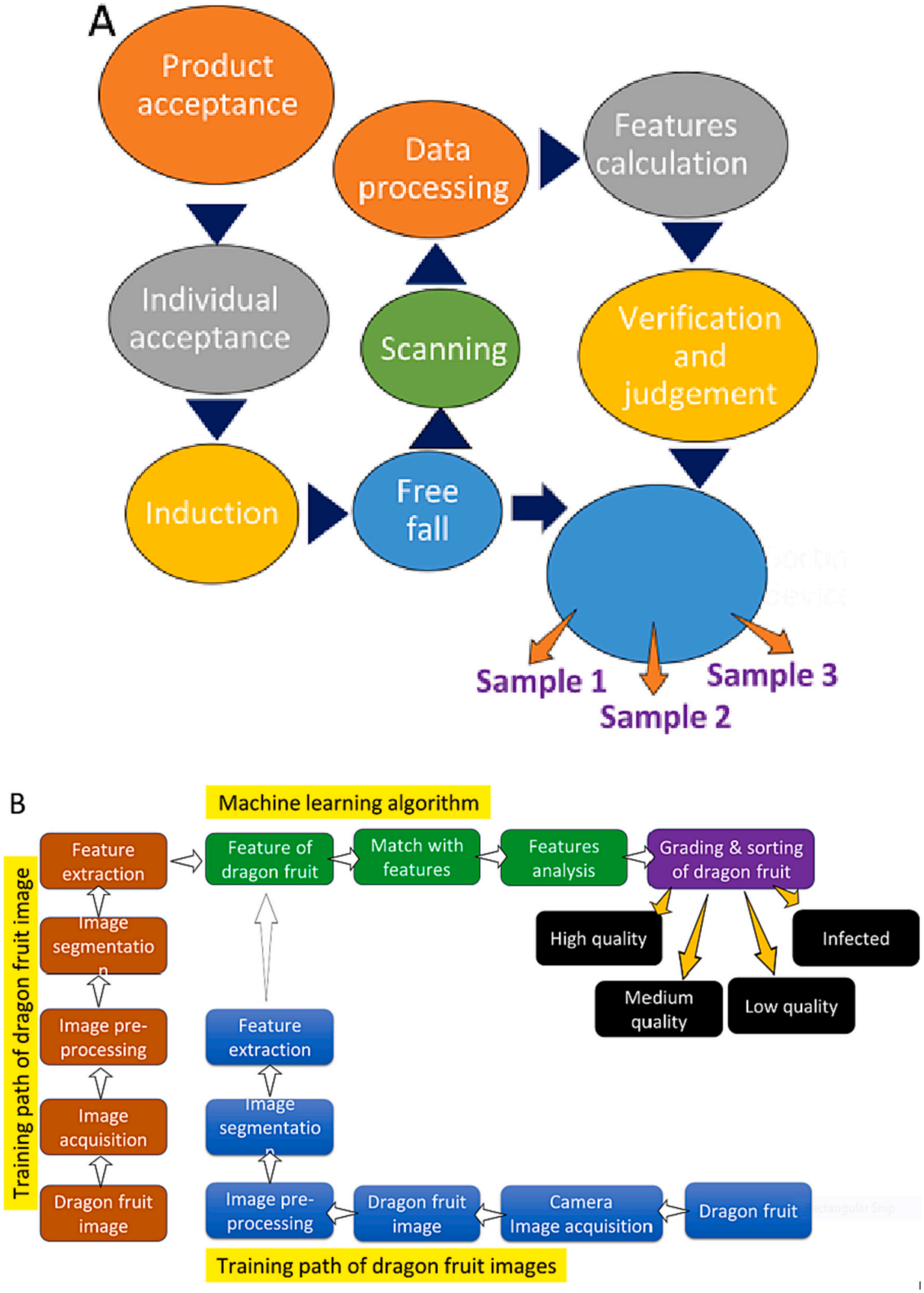

Fig. 5. Steps in the computerized separation of fruits and vegetables based on physical attributes. (A) Potato sorting and (B) Grading and sorting of dragon fruit. Panel B is reproduced from Patil et al. (2021) and is an open access article (copyright © 2023 Elsevier B.V., Amsterdam, the Netherlands) distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license.

concealed layer to withstand the challenging and complicated training. The FNN that handles optimization issues can be trained using BBO. This approach is known as BBO-FNN. The best load of FNN was determined using BBO, and at the conclusion, a sample yield assessment using stratified cross validation (SCV) was used. The classifier is trained using learning predictions, which then assist in predicting the requested fruit image (Yudong Zhang et al., 2016).

According to Patil, Lande, Nagalkar, Nikam, and Wakchaure (2021)

employs three ML algorithms like ANN, SVM, and CNN, to recognize and categorize dragon fruits based on their characteristics (Patil et al., 2021). As illustrated in Fig. 5B, the dataset of Dragon fruit images and camera captured Dragon fruit images perform image processing functions such as feature extraction for training, image pre-processing, image acquisition, image segmentation, and testing path of dragon fruit images. In order to reduce the rate of misclassification, the advanced computer vision-based fruit classifications system includes a digital camera, additional improvements for testing various fruit varieties, feed forward neural networks along with emerging world optimization technique, and biogeography-based adaptive control are used (Yudong Zhang et al., 2016). BBO is used in various fields with high efficiency results; now, they are using it in the food field to get accuracy.

Computer vision is a branch of AI, is needed for this automation. It employs various software programs to identify any damage in fruits and vegetables as well as classify them according to quality (Makkar, Verma, Yogesh, & Dubey, 2018). One of the greatest non-destructive techniques for illness detection is X-ray imaging technology. Mangoes, for instance, are evaluated for quality using Artificial Immune Systems (AIS), a technology created using X-ray imaging techniques (Addanki, Patra, & Kandra, 2022). The image processing system was created that uses images to evaluate, detect, and segment the physical features of mangoes, including colour, shape, size, and surface area (Abarna & Selvakumar, 2015).

3.4. Intelligent food packaging

In order to enhance the design, manufacture, and functional characteristics of packaging substances, AI and ML are increasingly employed in the packaging of food. On the basis of deep convolution generative adversarial networks (DCGAN), the packaging design model was used (Taneja et al., 2023). Visual communication technology can be used to improve a packaging design picture, leading to stronger visual communication abilities, a greater degree of image information fusion, and an enhanced packaging design. The inconsistent shape, colour, and size of fruits and vegetables make it difficult to design AI-based solutions in this industry. Therefore, large quantities of data are required to adequately train the system and enable it to carry out the work in a systematic manner. Drones and other intelligent tools can also play a big role in considerably lowering the cost of packing (Ahmad, Alvino, & Marino, 2022). Robotics, are being used for the automatic process of packaging, thereby lowering the demand for human labour and increasing the process speed and efficiency. To make sure that food goods are properly packaged and uphold quality requirements, robots may sort and examine them. Robotics are utilized to manage inventory, making sure that the materials needed for packing are available when required and lowering the possibility of shortages. Additionally, food products are delivered directly to consumers via drones, eliminating the need for packing and shipping.

3.5. New food product development

The first bioactive peptide in the world was released by a biotechnology business using AI technology. A special peptide network produced from rice protein is used as a sports nutrition supplement to reduce inflammation by altering cytokine responses and to enhance immune function. The business is the first in the world to show how AI can be used to improve human health. The AI-powered “home cooking sidekick,” a web and mobile application that combines with the smart kitchen helper “Hello Egg” to completely automate kitchen needs, has been released by another US-based IoT-focused technology start-up. The home assistant uses voice technologies to offer a diet strategy based on a person’s interests. Additionally, this may organize the pantry, classify the shopping list, provide video recipes, and help with grocery delivery (Taneja et al., 2023). The objective of sensory panellists working in the food and beverage industry is to sensory evaluating new foods in light of customer flavour preferences. Unfortunately, it might be challenging to predict the target group’s perceptions and preferences. This prompted businesses to create an effective approach for gauging and forecasting consumer preferences using an AI-based Gastrograph system that employs ML and predictive algorithms to comprehend market desire (Trencher, 2019).

3.6. Food fraud detection

In recent time, the use of AI to combat food adulteration has increased. AI for food adulteration detection includes managing data sets of real and fake products to train algorithms to detect minute compositional variations. These variations are involved in developing a model that can analyze the process of tempering food products by sensing the products. This technology has a great deal of promise for the identification of non-visible adulterants in a non-destructive manner. Additionally, using AI in adulterant detection is an efficient and cost-effective approach, mainly for a larger number of adulterants. However, when AI examines more samples of real and fake goods, its accuracy will eventually increase due to its capacity to learn from new data and adapt. An increasing number of food adulteration products including edible oil, and beverages are detected using AI.SVM was employed to evaluate the quality of agricultural and food products, such as detecting adulterants in cheese, seacucumber, tomato, blueberry, and adulterated processed meat (Zhao, Feng, Chen, & Jia, 2019). According to Geng et al. (2022) employed the detection of contaminated fishmeal, an association of 3D-digital microscope and CNN was used, with 93.3% efficiency (Geng et al., 2022). Based on hyperspectral imaging, the CNN model was built as a model for quality and quantity features prediction for mutton adulterated with pig or duck, and it reached 99.85% efficiency (Yaoxin Zhang, Zheng, Zhu, & Ma, 2022). Additionally, CNN has achieved 99.87% efficiency in identifying minced mutton adulterated with pig in thermal pictures from various classes. Similarly, Izquierdo et al. (2020) classified pure honey and contaminated honey using a thermo-graphic camera and CNN, with up to 95% accuracy. Additionally, CNN successfully distinguished photos from different classes depend on the several quantities of syrup with a classification rate efficiency of roughly 93% (Izquierdo et al., 2020). It’s important to note from these publications that CNN has successfully recognized photos and has advanced to the state of the art in image pattern recognition. Additionally, CNNs consistently outperformed traditional ML for both categories and regression (Geng et al., 2022). SVM and partial least squares (PLS) models were outperformed by the suggested CNNs in both classification and regression (Yaoxin Zhang et al., 2022). Using CNN to statistically predict the porcine content of tainted mutton and swiftly identify it in comparison to k-nearest neighbour’s algorithm (KNN or k-NN) and SVM. However, in the field of food adulteration, SVM has outperformed other ML techniques with more outstanding results (Li, Shepperd, et al., 2020). The findings showed that derivative-least squares-SVM (Der-LS-SVM) outperformed PLS-DA in terms of efficiency (97.05%), sensitivity (96.57%), and specificity (97.58%) when it came to honey adulteration detection. The authenticity and adulteration of food have lately been determined using AI methods (Table 1).

3.7. Analysis of food compositions and food image

The capacity to predict food components with sufficient accuracy has a significant impact on food safety, product development, and overall nutrition. Conventional methods for analyzing the composition of food need a lot of laboratory testing, are expensive, and require a lot of manpower. However, recent advancements in AI offer a fantastic opportunity to overcome these constraints and produce precise and effective food component forecasts. According to a new study, ANNs can predict the chemical composition of peach fruit with high accuracy, indicating that AI has practical applications in the food industry (Pulimamidi & Buddha, 2023; Gradxs & Rao, 2023). These results are in line

Table 1
Artificial intelligence techniques for verification and adulteration detection of various food products[1].

AI technique	Product	Instrument used	Objectives	Evaluation of performance (%)	References
ANN	Olive oil	FTIR and Vis-NIR	Quick detection of olive oil adulteration using soya oil	100	(Meng et al., 2023)
	Black tea	Spectrophotometry	Rapid carmine detection in black tea	100	(Wei, Yang, & Sun, 2020)
	Seasame oil	Dielectric spectroscopy	Quantification & classification of seasame oil adulteration	100	(Firouz, Omid, Babaei, & Rashvand, 2022)
	EVOO	Fluorescence sensors	Monitoring storage conditions and locate adulterations	91 to 100	(Lastra-Mejias et al., 2019)
	EVOO	Laser-diode induced	Cognitive authentication and fraud detection	MAE of 1.5% *w*/w	(Torreblanca-Zanca et al., 2019)
	Honey	MIR spectroscopy	Detection of sugar adulteration in honey	97.96	(Li et al., 2020)
	Mutton	Hyperspectral image	Adulteration identification	99.95	(Zhang et al., 2022)
	Wheat flour	Hyperspectral imaging	Adulteration in wheat flour	92.45	(Zhang, Zheng, Zhu and Ma, 2022)
Deep learning (CNN)	EVOO	Optical microscope	Detection of adulteration of EVOOs with vegetable oils	96	(Pradana-Lopez, 2022)
	Honey	RS	Sugar adulteration identification and quantification in honey	94.76	(Wu et al., 2024)
	Avocado oil	Optical image	A refined adulterant mixed into pure avocado oil was thoroughly quantified	95	(Pérez-Calabuig, 2023)
	Peanut	Hyperspectral image	Aflatoxin detected in peanuts	96	(Han & Gao, 2019)
	Coffee	FT- NIR spectroscopy	Predict the adulteration of food	$R^2 > 0.99$	(Chakravartula, 2022)
	Milk powder	LIBS	Identification of adulterated milk powder	97.9	(Huang, 2022)
	Meat	Digital image	Classify and quantify mutton adulteration with pork	82.13	(Zhang et al., 2022)
	Beef	Hyperspectral image	Beef adulteration prediction using spoiled beef	$R^2 = 0.94$	(Zhao et al., 2019)
	Honey	ATR-FTIR	Adulteration of honey with rice syrup detected	97.08	(Li, Shepperd, et al., 2020)
	Cassava-starch	RS	Detection of cassava starch for adulteration	86.8	(Cardoso & Poppi, 2021)
	Seasame oil	Near-mid infrared spectroscopy	Sesame oil differentiation from corn oil	100	(Yang et al., 2020)
SVM	Saffron	Electronic-nose	Saffron adulteration detection	Aroma: 100 &colour: 89	(Kiani, Minaei, & Ghasemi-Varnamkhasti, 2017)
	Pure fishmeal	NIR-hyperspectral imaging	Detection of marine fishmeal adulteration	99.43	(Kong, 2022)
	Butter oil	NIR-spectrometer	Predicting butter oil quality characteristics and levels of adulteration	90	(da Silva Medeiros, 2023)
	Sea cucumber	Hyperspectral image	Detection of salted sea cucumber adulteration	97.98	(Zhang, 2021)
	Milk	IR-spectrophotometer	Detection of melamine in adulterated milk	99.04	(Jin, 2023)
SVM & ANN	EVOO	LIF	Olive oil adulteration is portablely detected and quantified	100	(Mu, 2016)
Random forest	Ground nutmeg	IR-spectroscopy	Ground nutmeg and evening primrose oils have been found to be adulterated	99	(de Santana, Neto, & Poppi, 2019)

[1] ANN: Artificial neural network; EVOO: Extra virgin olive oils; SVM: Support vector machine; RS: Raman spectroscopy; Vis-NIR: Visible-near-infrared; FTIR: Fourier transform infrared; LIF: Leasure induced fluorescence; IR: Infrared; NIR: Near infrared; MAE: Mean absolute error; e-nose: Electronic nose; CNN: Convolutional neural network; LIBS: Laser-induced breakdown spectroscopy; ATR: Attenuated total reflection.

with the observation that ANN predicts the phenolic and flavonoid content of garlic more correctly than the response surface technique does. Dietary assessment is fraught with a multitude of research and personal challenges. Several techniques have been developed for evaluating food and meal patterns, but all of them rely on participants providing their own information. One such technique is principal component analysis. Deep learning algorithms for food picture recognition are among the novel approaches that are becoming more and more necessary as food databases get bigger. The "NutriNet" tool, for example, was created and meticulously evaluated using over 225,000 images of 520 distinct foods and beverages; in contrast, the GoCARB app performed as well in crab estimation as dieticians (Pulimamidi & Buddha, 2023; Buddha, Kumar, & Reddy, 2022; Manikyam, McDonald, Mahoney, Andel, & Russ, 2016). The goFOODTM software could approximate the number of calories and macronutrients in a given meal based only on photographs from a smartphone. Thus, nutritional assessment in human studies could benefit from these new tools.

3.8. Development of personalized nutrition

AI makes it easier to design customized meal plans. Diverse phenotypic reactions to certain therapies may be explained by various biochemical, metabolic, genetic, and gut bacterial components; this is a consequence of a customized approach. AI and bioinformatics may be used to identify biomarkers connected to certain dietary interventions or health outcomes (Boland, Alam, & Bronlund, 2019). The aforementioned aid in both a better understanding of the molecular mechanisms underlying nutrition-related illnesses and the development of targeted therapeutics. The integration of bioinformatics' computational power with artificial intelligence's sophisticated algorithms and learning capabilities enables researchers to improve our understanding of nutrition-related phenomena, create customized treatments, and offer evidence-based recommendations to optimize human health and wellbeing.

3.9. Gut and gut microbiota

The application of artificial intelligence methodologies may be utilized to investigate the connections between gut flora and nutrients. It is important to note that researching the different effects of probiotics can help develop probiotic combinations, single strains, and even synthetic strains using synthetic biology techniques. Furthermore, other sophisticated tailored models have been developed, such as the "enbiosis model," which is believed to be reasonably successful in producing individualized meal programs to improve microbiome (Simhadri & Chaitanya, 2023; Vaddadi, Arnepalli, Thatikonda, & Padthe, 2022). In a pilot clinical trial, this AI-assisted eating plan considerably reduced

symptoms of irritable bowel syndrome when compared to a control diet. Cardiovascular risk prediction models were greatly improved by using AI-powered algorithms that incorporate gut microorganisms.

4. Applications of AI in agricultural industry

Nearly every industry is being affected by innovations like the Internet of Things (IOTs), big data &analytics, AI, and ML. Through "smart farming," efforts are being made to make agricultural products more "connected" and "intelligent" in order to increase their quality and quantity (Tavill, 2020). The influence of AI on the Argo-food sector and FMCG is shown in Fig. 6A. Several ML technologies that were implemented in the agricultural sector have improved crop management modern imaging. The AI methods use ML algorithms to examine grain pictures and spot flaws or contaminants like cracked kernels, foreign objects, or fungi. The agricultural grains were identified and classified effectively using ANN, dense scale-invariant feature transform (DSIFT) method, and SVM. ANNs are employed to categorize various wheat species according to their visual traits, such as form, size, and colour (Sabanci, Kayabasi, & Toktas, 2017). The DSIFT method is a computer vision technique that can recognize characteristics of wheat grains, such as their size, shape, and texture, and use these to classify the grains into several groups. Another ML method is SVM, which is used to classify wheat grains, identify fungal species in rice, analyze milled rice grains, and analyze wheat grains that have germinated. The weed *Silybum marianum* was detected using unmanned aircraft systems (UAS) and counter propagation-ANN (CP-ANN) (Rejeb, Rejeb, Zailani, Keogh, & Appolloni, 2022).In order to find and identify weed species in agriculture fields, it can be highly helpful to use ANN and multi-spectral or hyperspectral imaging technology. The weed *Silybum marianum* was discovered using CP-ANN and multispectral images taken by UAS (Pantazi et al., 2017). Multispectral imaging entails taking pictures of crop fields at various light wavelengths, whereas CP-ANN is a kind of ANN that is utilized for pattern identification applications. In another study Binch and Fox (2017), a system for identifying crop and weed species was developed using hyperspectral imaging and ML approaches. By capturing the agricultural fields using a variety of light wavelengths, a process known as hyperspectral photography, it is possible to learn more about the spectral characteristics of various plant species. Then, after analyzing these photographs and categorizing various plant species, including crops and weeds, ML algorithms were applied. The classification of various weed kinds in grassland cropping systems has also been established by researchers using an SVM-based algorithm using photos from unmanned aerial vehicles (UAVs) (Binch & Fox, 2017). Strawberry harvesting is a labour and time-intensive activity that can be automated with robots like the Berry 5 Robot from Harvest Croo-Robotics (Tampa, FL, USA) (Xiong, Ge, Grimstad, & From, 2020). More quickly than a human, the robot can identify and select ripe strawberries using computer vision and ML techniques. It can improve the harvesting efficiencies of strawberries; this can help farmers cut labour costs and increase yields. Similar to this, robots like the "Robocrop" are being created for particular agricultural jobs, such pruning strawberry plant blooms.

Additionally, the image-processing robot being created to harvest matured strawberries employs computer vision and ML algorithms to recognize and choose the strawberries, lowering labour costs and enhancing the speed and efficiency of the harvesting operation. The IoTs, a new technological device that allows connection under remote conditions and enables smart farming. AI advocates the replacement of traditional agricultural methods and techniques with smart farming, a sustainable strategy that helps prevent resource waste and maintain the sustainable growth (Rejeb et al., 2022). Smart farming ensures the farmers about the adequate judgment of crops to improve their production by giving them extensive knowledge on particular crops; nutritional deflects of soil, moisture levels, and hyper-spectral data to minimize damage. Research indicates that the market for supply chain big data analytics would increase to $9.28 billion by 2026 (Taneja et al., 2023). Agricultural technology start-ups using AI technologies is illustrated in Table 2.

Applications built on ML can calculate evapotranspiration on a daily, weekly, or monthly basis, enhancing the efficiency of irrigation systems. AI systems are able to predict weather patterns, evaluate the health of crops, and identify illnesses, pests, and inadequate plant nourishment. Using drones with AI technology, farmers can keep an eye on the health of their crops. The most time-consuming and physically taxing farm jobs are already being handled by some farmers utilizing agricultural robots. These machines can lighten the workload of workers and enable farmers to save money on physical labour. Fig. 6B shows a potential project using ML to anticipate crop yield based on climate trends and vegetation indices from remote sensing. Climate records and regional or field imaging for the places and crop whose yield are want to forecast are required in the case of yield forecasting based on climatic factors and vegetation indices. A "supervised-learning" technique would be used in this instance because we are fairly certain which climate variables are crucial for crop yield. Precipitation totals, air temperatures, degrees of water stress, accumulation of growth degree-days, and NDVI (normalized difference vegetation index) are among the climatic and remote sensing indicators utilized as input to the model, as illustrated in Fig. 6B. The NDVI and other vegetation indices are computed using data captured by sensors installed on a variety of platforms, including satellites, aircraft, and drones. Because they include details regarding plant health, canopy coverage, and/or water status of canopies, NDVI values estimated during the cropping season aid in the yield forecasting process.

4.1. Effect of selected models on the crop classification performance

A study by Wang et al. (2022) evaluated the influence of several CNN designs with varying number of layers on plant categorization from optical pictures captured by Unmanned Aerial Vehicle (UAVs). They suggested a CNN-based architecture that beat state-of-the-art CNN designs, with FDN-17, FDN-29, and FDN-92 obtaining overall accuracy of 86%, 84%, and 87%, respectively, compared to 80%, 76%, and 82% for Inception-V1, ResNet-101, and Dense-Net-121 (Wang, Liu, et al., 2022), respectively. Another studyby Morales et al. (2018) examined the effects of the chosen U-Net-based topologies on overall categorization performance (Morales et al., 2018). Similarly, YOLOv3 outperformed the RetinaNet detector in terms of performance, which were trained on the same dataset and achieved an average precision of 79.85% compared to 73.41% for the RetinaNet (Bouguettaya, Zarzour, Kechida, Taberkit, & Applications, 2022). This is likely owing to the two detectors' distinct backbone topologies, DarkNet-53 for YOLOv3 and ResNet for RetinaNet. Furthermore, the authors Fuentes-Pacheco et al. (2019) develoed a SegNet-based architecture with fewer layers, resulting in fewer trainable parameters, making it quicker and more straightforward (Fuentes-Pacheco et al., 2019). Because of the two detection steps, Faster R-CNN has the slowest inference time of 163 ms/image, making it unsuitable for real-time operations or compact devices. However, as expected, one-stage algorithms (YOLOv3 and Retina Net) acquired the lowest computational cost, allowing for real-time detection. According to CrowNet that depends on the SegNet architecture outperforms the Mask Scoring R-CNN architecture in maize crop row segmentation attaining accuracy rates of approximately 85% and 83%, respectively (Pang et al., 2020). However, the decreased precision supplied by Mask Scoring R-CNN may be attributed to the greater flying altitude, which ranges between 40 and 60 m over the ground's surface. Furthermore, the created model received instruction on only two developing stages (V4 and V5), which may have an impact on its ability to detect maize crop rows at subsequent growth stages. Also, Yang, Tseng, Hsu, and Tsai (2020) studied the FCN method outperformed SegNet with an F1-score of 83.21% and an inference time of 72 s per image, while SegNet attained only 69.36% and an inference time of 106 s per image (Yang et al.,

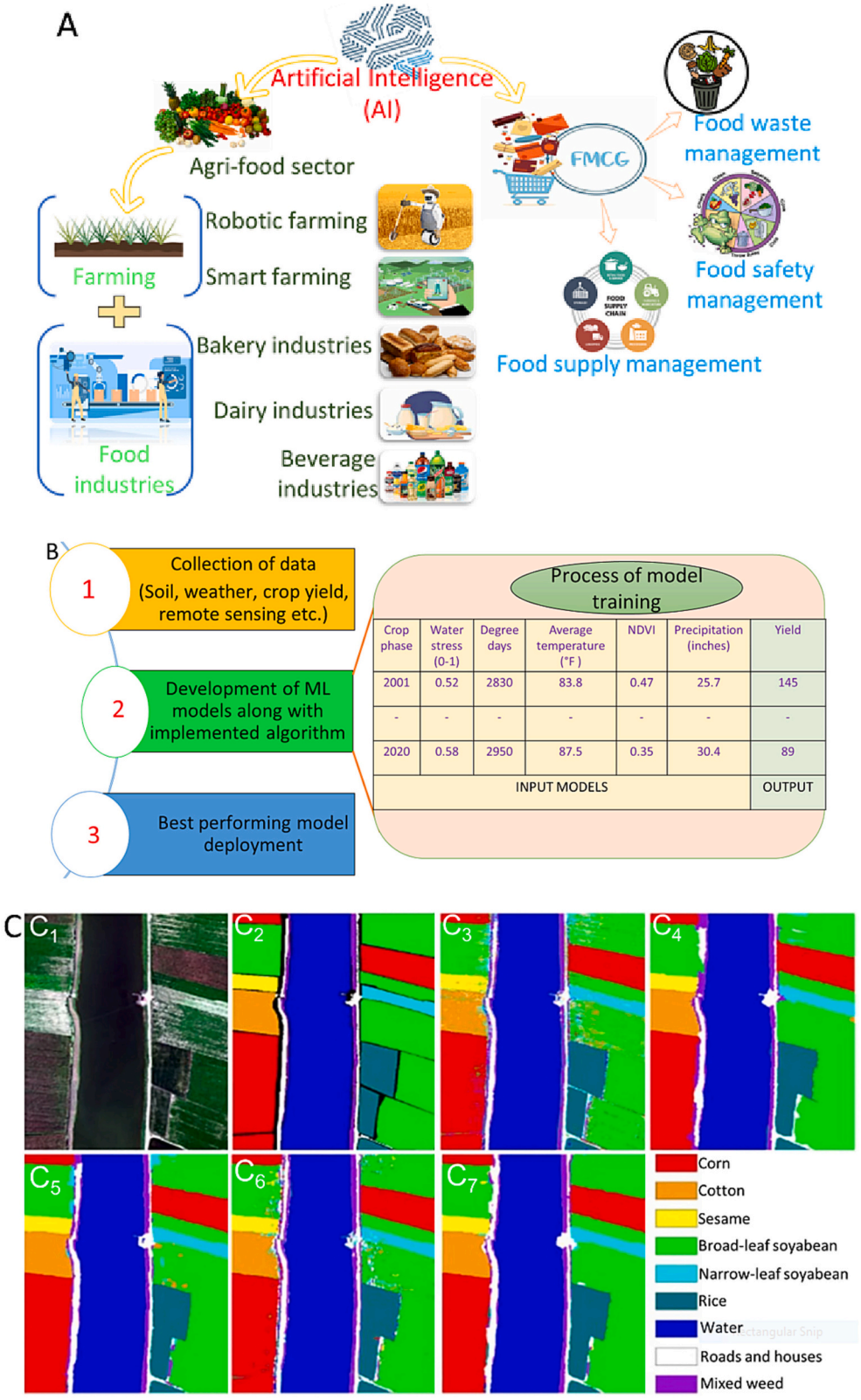

Fig. 6. Application of artificial intelligence and machine learning in agro-food industry. (A) Fast-moving consumer goods (FMCGs) industry, (B) Forecasting crop yield based on climatic patterns and remote sensing-based vegetation indices based on supervised learning, and (C) Comparison of different algorithms to classify crop types: (C_1) true-colour image, (C_2) ground-truth image, (C_3) support vector machine, (C_4) fractal net evolution approach for object-oriented, (C_5) support vector conditional random field classifier with a Mahalanobis distance boundary constraint, (C_6) benchmark convolutional neural network, and (C_7) convolutional neural network-conditional random field. Panel B is reproduced from Fraisse et al. (2022) and is an open access article (copyright © 2022 by authors) distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license, while Panel C is reproduced with permission (copyright © 2022, the author(s), under exclusive license to Springer-Verlag London Ltd., Springer-Verlag London Ltd., part of Springer Nature, Berlin, Germany) from Bouguettaya et al. (2022).

Table 2
Agricultural technology start-ups using artificial intelligence technologies[1].

AI Technology	Entity	Objectives	Details	References
Smart irrigation	*Hydro point and data system*	*Evapotranspiration technologies and intelligent methods of irrigation*	*Founded in 2002, USA*	(Hergert, 1998)
	Alesca Life	*Fresh on-site creation of difficult-to-find microgreens and wheat grass using a vision and data-driven system*	*Founded in 2013, China*	(Gade, Gade, & Reddy, 2016)
	Aquaspy	*Monitoring crop behavior with respect to water and nutrients by use of modelling based on anticipated soil moisture parameters*	*Founded in 1998, Australia*	(Sloane, 2007)
Sensors	*Sencrop*	*Use sensors to make accurate and effective predictions, such as rain and wind gauges*	*Founded in 2016, France*	(Foubert & Mitton, 2019)
	Spensa Technologies	*Intelligent sensors for weed identification and pest forecasting*	*Founded in 2009, USA*	(Caplan, 2014)
	Centaur Analytics	*Reducing needless chemical use by employing sensors to monitor individual crops*	*Founded in 2014, USA*	(Dian, Vahidnia, & Rahmati, 2020)
Robotics/ Droners	*Blue River Technology*	*Identifying the health of crops through drone imaging*	*Founded in 2011, USA*	(Bharambe, Singh, & Binsale, 2020)
	Sky Squirrel Technologies	*Weed control resistant to herbicides Automated vehicles and cloud computing for higher yields*	*Founded in 2012, Canada*	(Singh et al., 2020)
	Ceres imaging	*Analyze nutrient inadequacies, create a management zone, permit variable rate application, and monitor water stress.*	*Founded in 2014, USA*	

[1] AI, Artificial intelligence.

2020). Furthermore, SegNet has a very high false detection rate with a recall rate of <30% when using RGB? Ex-G? ExGR data and a GSD of 5.7 cm/pixel. However, Song et al. (2020) in the instance of sunflower crop classification, SegNet architecture delivers somewhat higher overall accuracy than FCN (Song et al., 2020). Similarly, Bah, Hafiane, and Canals (2019) discovered that the FCN architecture performs quite poorly at detecting beet rows (Bah et al., 2019). Fig. 6C depicts a comparison of different algorithms used to classify distinct crop varieties.

5. Sustainability of AI in agro-food industry

SVM and ANN models were used to support modern ML-based food processing technologies that detected the presence of nitrosamine in red meat food samples (Arora & Mangipudi, 2021). Furthermore, AI-powered cucumber harvesting robots with computer vision systems and hardware such an autonomous vehicle, a manipulator, and an end-effectors have been developed. These robots can accurately detect and image the ripeness of cucumbers (Van Henten et al., 2002). Moreover, AI has demonstrated its efficacy in enhancing the physical fields of microwave, radio frequency, infrared radiation, and ultrasonic fields used in the drying process of fresh foods, fruits, and vegetables (Sun, Zhang, & Mujumdar, 2019). For instance, employing AI to detect and control the drying process online helps cut down on energy use, eliminate uneven drying, enhance sensory assessment, and minimize nutritional loss (Chen, Zhang, Xu, Sun, & Mujumdar, 2020).

To provide one more illustration, (Amani & Sarkodie, 2022) offered a method for detecting rotten meat using deep learning, which is a significant contributor to food waste and greenhouse gas emissions. Traditional methods of managing the supply chain for meat, prevalent in many developing countries, rely on non-intelligent equipment and manual monitoring that is prone to human error. Reducing waste and halting the spread of pathogens require early detection of bad meat. AI is able to instantly discern between fresh and rotten meat thanks to deep learning and image processing. These AI systems practice on various images of meat to learn how to detect decaying (Zheng, 2022).

The study demonstrated how well machine learning techniques can predict important soil metrics including total nitrogen, organic carbon content, and moisture content (Morellos et al., 2016). Furthermore, ML algorithms have shown to be beneficial for streamlining irrigation procedures, improving crop quality and quantity, and skill fully handling drought conditions when included into smart irrigation systems (Goap, Sharma, Shukla, & Krishna, 2018). To maximize water resources, smart farms use automated irrigation systems that keep an eye on and manage water tanks, chamber and open irrigation systems. Crop management with AI starts at seeding and continues with crop development, harvesting, storage, and distribution monitoring. Many ML algorithm models are available for predicting the weather (Saggi & Jain, 2019), crop protection (A. Singh, Shukla, & Mishra, 2018), weed detection (Liakos, Busato, Moshou, Pearson, & Bochtis, 2018), crop quality management (Chlingaryan, Sukkarieh, & Whelan, 2018), and harvesting (Sadgrove, Falzon, Miron, & Lamb, 2018). An in-depth understanding of weather patterns facilitates decision-making, which raises agricultural yields of superior quality (Aubry, Papy, & Capillon, 1998). The information or data collected by AI agents is analyzed by deep learning algorithms and AI-powered systems, making it easier to monitor the health of crops and soil (Morvan et al., 2008). Studies have shown that artificial intelligence and image processing have made substantial progress in tackling the problem of weed identification (Karimi, Prasher, Patel, & Kim, 2006). These earlier research demonstrate the potential of AI models, in particular SVM, to increase crop output through timely interventions by showing that SVM is excellent at early stress diagnosis during crop growth and efficient at identifying optimal nitrogen delivery rates (Karimi et al., 2006). Furthermore, a study emphasizes the financial importance of minimizing profit and yield declines associated with weeds (Neil Harker, 2001) and highlights the role of AI and ML in addressing spatial heterogeneity and its impact on crop yield (Swanton, Nkoa, & Blackshaw, 2015). The application of AI-based technology in food production and agriculture may benefit the environment, according to research findings (Alamu, Menkir, Adesokan, Fawole, & Maziya-Dixon, 2022). By 2030, these technologies might, for example, save over 300 billion liters of water, enhance crop yields by up to 30%, and cut yearly oil usage by 25 million barrels (Strategy, 2015).

6. Challenges and future trends

According to the United States Department of Agriculture (USDA), food, agriculture, and other related industries contributed $1.109 trillion to the U.S. GDP in 2019. Yet AI is not utilized widely throughout these large sectors. The adoption of AI in the food industry is boundless and will drive process efficiencies and customizable experiences. It will undoubtedly have an impact on the economy and daily life. A variety of AI technologies, such as expert systems, ANNs, DL, and FL, can be used to identify the quality of agriculture and food items. Various hybrid non-destructive approaches, including the e-nose, computer vision systems, and spectroscopic techniques, have been merged for real-time monitoring in problem resolution connected to quality of food, taking into account the distinctions of these AI tools. In addition, the reliability and computational efficiency of the entire system could be improved by combining mathematical models, export systems, ANNs, DL, and FL.

There isn't a single algorithm that can fix every issue. For a model to be effective, the best learning algorithm must be chosen for the specific task at hand. The goal of further studies should be to create a framework architecture where algorithms tested and trained for a specific use (such as identifying certain flaws in agricultural output and identifying food adulteration) are suggested for future employed in practice. Depending on the dataset, one or more methodologies or numerous instrumental approaches may be used in terms of data processing. In this manner, integrating numerous types of sensors can be difficult since it necessitates collecting data from many types of sensors and examining the advantages and disadvantages of each sensor in a specific application.AI has been effectively used to evaluate quantitative analyses of fruit deterioration, including mechanical damage and chilling injury. These approaches often rely on an experimentally determined severity index, either by direct induction through an experimental process or through the temporal progression of the defect. Using learning techniques, the distinction between the various levels of deterioration picked up by objective, non-destructive measuring tools was clarified. The quantification of damage and disorders, which is still a difficult problem in the agriculture business and calls for more focus on employing learning algorithms in the future, is another field of study that sophisticated AI algorithms have not yet fully investigated.

First and foremost, the biggest social issue facing society is potential unemployment. As intelligent machines and robots have the potential to replace most monotonous jobs and tasks, human intervention in the labour market is decreasing, which will pose a serious danger to employment standards. Other technical difficulties include the fact that machines can only perform functions for which they are designed or programmed; if they are used for anything else, they frequently malfunction or provide results that are not relevant. Furthermore, the high expenses associated with developing and maintaining intelligent machines and clever computers may be viewed as technological barriers to AI advancements. This is particularly true given that AI is constantly evolving, necessitating regular updates to hardware and software in order to stay up to date. Equipment requires costly upkeep and repairs. Because they are extremely complicated machines, their creation comes at a significant expense. The high cost of these applications, which could raise the price of the items, is another problem. Furthermore, in addition to the advantages that smart and computerized technologies provide, there are potential risks and concerns that could affect sustainability. These include the enormous energy consumption, the e-waste issue, market concentration, employment displacement, and even the ethical framework (Patelli & Mandrioli, 2020).

7. Conclusions

AI integration in agricultural and food processing has the potential to completely transform these sectors, providing various advantages in terms of productivity, sustainability, and quality. Throughout this study, the application of AI throughout the entire food processing environment is addressed, including beverage manufacturing from fruits, vegetable processing, dairy sector processing, crop production, and its significance in intelligent food packaging are discussed. It lowers the risk of food borne illnesses and ensures product quality by detecting pollutants, and spoilage in food products. AI can help with traceability as well, making it possible to quickly identify and remove contaminated products from the market. Similarly, in the agricultural industry, AI has played an important role in crop yield optimization, herbicide and fertilizer optimization, crop and weed detection, and fruit harvesting. AI models are effective in classification of crop. Global population is predicted to exceed 9 billion by 2050, necessitating a 70% increase in agricultural production to satisfy the demand. Only around 10% of this enhanced production may come from empty lands, with the remainder to be fulfilled by present production intensification. In this environment, the deployment of cutting-edge technical solutions to increase agricultural efficiency remains critical. Current tactics for increasing agricultural productivity necessitate large energy inputs, yet the market expects high-quality food. Robotics and artificial intelligence are expected to change the global industry that enables the increase production of agri-food products (from farm to retail shelf). These technologies will have a significant impact on major sectors of the economy with low productivity. Overall, the incorporation of AI into agri-food systems holds immense potential in addressing key challenges within agriculture, fostering sustainability, and contributing substantially to global food security. As we celebrate one year of progress, it is evident that AI continues to be a driving force in reshaping the future of agriculture and food industry.

CRediT authorship contribution statement

Pinku Chandra Nath: Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Awdhesh Kumar Mishra:** Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Ramesh Sharma:** Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Biswanath Bhunia:** Writing – review & editing, Validation, Software. **Bishwambhar Mishra:** Writing – review & editing, Validation, Software. **Ajita Tiwari:** Writing – review & editing. **Prakash Kumar Nayak:** Writing – review & editing. **Minaxi Sharma:** Writing – review & editing. **Tamanna Bhuyan:** Writing – review & editing. **Sushant Kaushal:** Writing – review & editing. **Yugal Kishore Mohanta:** Writing – review & editing, Visualization, Validation, Supervision, Software, Resources, Project administration, Funding acquisition, Conceptualization. **Kandi Sridhar:** Writing – review & editing, Visualization, Validation, Supervision, Software, Resources, Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Food Production, Processing and Nutrition

REVIEW

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Postbiotics: the new horizons of microbial functional bioactive compounds in food preservation and security

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Abstract

In recent decades, consumers, manufacturers, and researchers have been more interested in functional foods, which include probiotics, prebiotics, and postbiotics. Probiotics are live microbes that, when regulated in enough quantities, provide health benefits on the host, while the prebiotics are substrates that host microorganisms selectively use. Postbiotics are metabolites and cell-wall components that are beneficial to the host and are released by living bacteria or after lysis. Postbiotic dietary supplements are more stable than probiotics and prebiotics. Many bioactivities of postbiotics are unknown or poorly understood. Hence, this study aims to present a synopsis of the regular elements and new developments of the postbiotics including health-promoting effects, production, conceptualization of terms, bioactivities, and applications in the field of food safety and preservation. Postbiotics aid in bio preservation and the reduction of biofilm development in food due to their organic acids, bacteriocins, and other antibacterial activities. The present study examines the production of postbiotic metabolites in situ in food and the effects of external and internal food components. The antimicrobial roles, removal of biofilms, and its applications in preservation and food safety have also been discussed. This paper also explored the various aspects like manipulation of postbiotic composition in the food system and its safety measures.

Keywords Food and health, Food safety, Probiotics, Postbiotics, Bio preservation

†Bishwambhar Mishra, Awdhesh Kumar Mishra and Yugal Kishore Mohanta contributed equally and treated as joint first authors.

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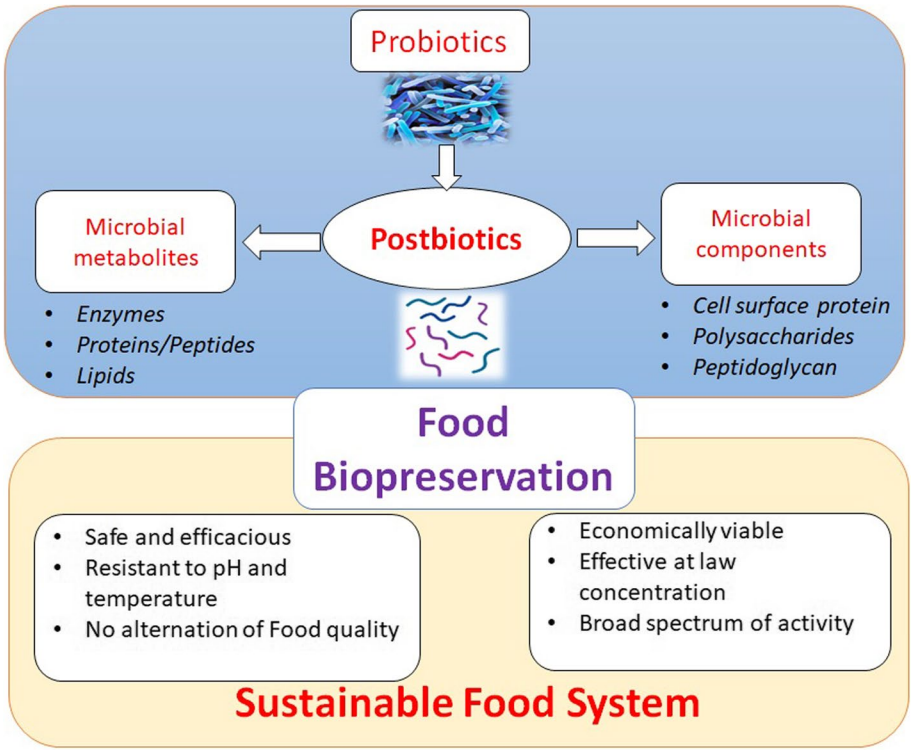
Graphical Abstract



Introduction

Numerous elements, such as physical, chemical, and biological threats, compromise food safety. Biological hazards are of the utmost relevance in this regard. Bacteria, for example, play key roles in food decomposition and food-borne disease transmission. Probiotics and their byproducts are examples of bioactive compounds that can be used to suppress harmful microorganisms growth and thus lengthen the lifespan of food products (Singh et al. 2019). Due to their substantial antibacterial effects, probiotics and postbiotics have been used to prevent the proliferation of pathogenic microorganisms and their mediated corruption. Recent research suggests that postbiotics may be suitable replacement ingredients for the probiotic cells and also can be used as innovative antibacterial agents (Nataraj et al. 2020). Healthy effect and adverse effect of probiotic for host health has been illustrated in Fig. 1.

As per the statement defined by expert group of FAO-WHO 2006, probiotics are "live bacteria, which when provided in suitable proportions, impart a health benefit on the host" (https://www.fao.org/3/a0512e/a0512e.pdf). Moat probiotic supplements contain a finite list of microbial taxa, principally lactic acid bacteria (*Bifidobacterium* spp., *Lactobacillus* spp.), which are considered safe (GRAS). On the other hand prebiotic is defined as "a substrate that is selectively used by host bacteria giving a health advantage" (Binda et al. 2020). Prebiotics can modulate the microbiota framework by boosting species growth, which benefits the host. Synbiotics are frequently characterised as "synergistic mixes of probiotics and prebiotics that benefit the host by enhancing the survival and colonisation of live beneficial bacteria in the host's gastrointestinal tract" (Roberfroid et al. 2010). Synbiotics can modify the configuration of the microbes present in digestive system and the synthesis of microbial metabolites. Postbiotics are any substances that are released by a microorganism or made by it as part of its metabolic process and have a beneficial upshot on the host, directly or the other way. Since postbiotics don't have live microbes, the risks that come with them are lower (Binda et al. 2020; Salminen et al. 2021b). However, one concern that arises in connection with the use of the probiotics is the presence of the antibiotic-resistant genes in certain strains of probiotics (Thorakkattu et al. 2022; Vinderola et al. 2022). This is because these strains can implicit to transport antibiotic-resistant genes

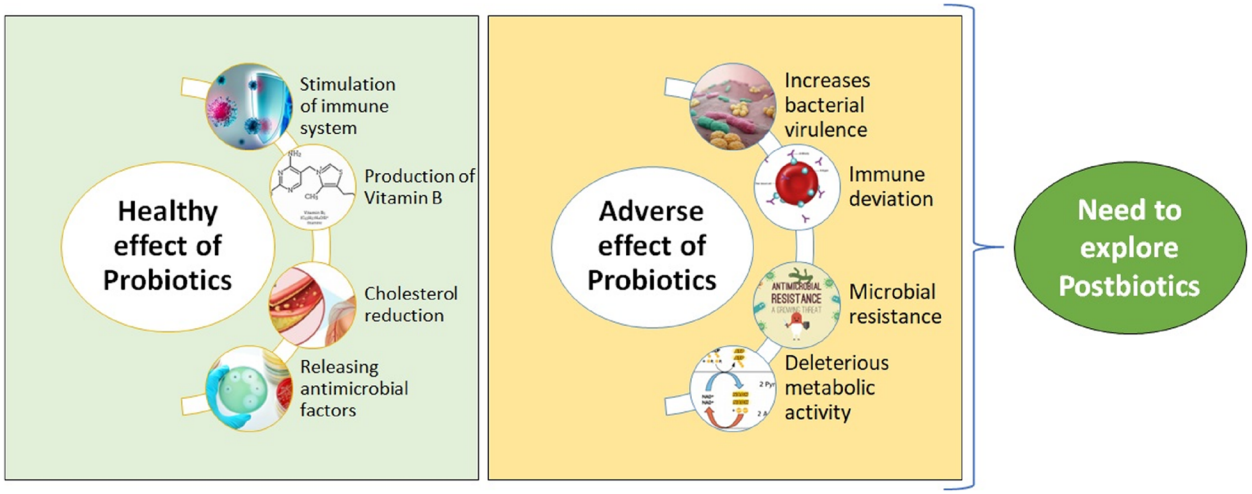


Fig. 1 Healthy effect and adverse effect of probiotic for host health

to infectious microbes through the process of horizontal gene transfer (Puccetti et al. 2020). Because of this lack of stability in the probiotics, the health advantages that are supposed to be offered by probiotic supplements may not be achieved. A significant percentage of postbiotic research is presently devoted to the growth of innovative functional foods and preventive medication formulations for improving host health, also the exact identification of their mechanisms of action. A broad range of bioactive food items, such as probiotics, dairy/ non-dairy products, are currently in the market to meet the needs of clients' nutrition with different dietary choices, especially those who are hypersensitive to milk peptides, lactose intolerance, and vegetarians (Moradi et al. 2020; Ozma et al. 2022; Wegh et al. 2019). Correlation with definition of probiotics, prebiotics, symbiotics, and postbiotics has been illustrated in Fig. 2.

The idea emerged that postbiotics obviate the requirement for conventional intake of substantial quantities of microorganisms (Rad et al. 2021). Also, the use of postbiotics can be done in a controlled and standardized way. However, when living bacteria are used, the level of toxicity is much lower because the size and function of the active structure in the digestive system are directly related to the number of strains and the level of metabolic activity, they show (Aguilar-Toalá et al. 2021; Nataraj et al. 2020; Tsilingiri & Rescigno 2013). Postbiotics have a number of advantages, including greater immunological and digestive health. In addition to having anti-inflammatory, immune-modulating, antioxidant, anti-hypertensive, and anti-obesity, postbiotics also have beneficial qualities. A significant amount of research, encompassing both animal and human trials, has yielded encouraging findings about the efficacy of postbiotics in addressing obesity. For example, studies utilizing kefir products enriched with postbiotics have shown positive effects on body weight, fat mass, and metabolic indicators in both animal models and human subjects. Furthermore,

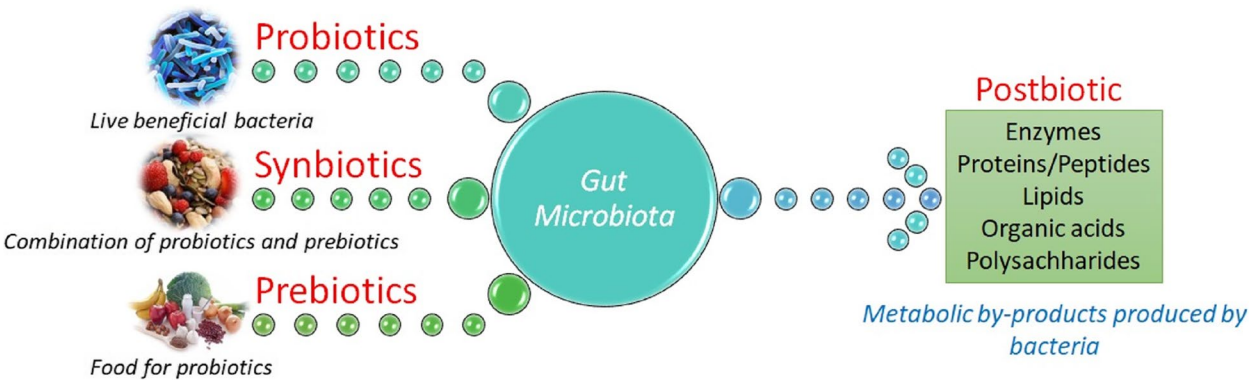


Fig. 2 Differentiating and defining probiotics, prebiotics, symbiotics and postbiotics

empirical research has demonstrated that certain postbiotics possess the ability to regulate the composition of the gut microbiota, hence promoting the proliferation of advantageous bacteria that are linked to the regulation of body weight (Dini & Mancusi 2023; Park et al. 2023).

Postbiotics are appealing for commercial uses due to their non-toxic, easy-to-transport, less expensive-to-store, and up to five-year shelf-lives as well as their cholesterol-lowering and antiproliferative capabilities. Postbiotics such as bacteriocins, organic acids, fatty acids, peptides and H_2O_2 molecules are what give them their antibacterial capabilities. Vitamins produced by probiotic mother strains, especially vitamin C, are helpful in suppressing pathogenic ones. It has a substantial influence on the microbiota structure, the gut ecosystem, barrier function, immune system development, and all of these things. Thus, postbiotics may be useful in management or prevention of a variety of disease entities, including those for which no curative therapy for the underlying cause has yet been identified, such as multiple sclerosis, inflammatory bowel disease or Alzheimer's disease. Clinical studies are being conducted, and the preliminary findings are encouraging. These studies are looking at how to alter the microbiome of people who have the aforementioned diseases (Aguilar-Toalá et al. 2018; Collado et al. 2019; Salminen et al. 2021a). Given the importance of the initial few months of life for the development of the proper microbiota structure, postbiotics can be especially helpful for infants. For the appropriate growth and safeguarding the child's ultimate welfare, the right postbiotic settings for the generation of the right microbiota appear to be required (Ashraf & Shah 2014; Johnson et al. 2019). Postbiotics may be beneficial for the avoidance and treating of SARS-CoV-2 infections because the morphology and metabolic functions of the gut microbiome can be connected with the emergence of the biomarkers that anticipate the course of extreme coronavirus disease- 2019 (COVID-19) (Rather et al. 2021).

The food industry has always been focused on using preservatives to enhance quality and prolong its shelf life. However, most people today dislike food additives because they think they are unhealthy, despite the fact that they don't know how the additives have on health. Because of this, modern research has been trying to come up with products which uses lesser additives or natural ingredients to make sure food is safe and of good quality while still meeting consumer needs. In this way, researchers have paid a lot of attention to natural antimicrobial agents, which have made it possible for manufacturers to switch from using artificial additives and make safer and healthier foods. Several Lactic acid bacterial strains can be thought of as probiotics, and their postbiotic substances often have the same or similar health benefits for consumers. Postbiotics can be used to maintain and eradicate bacterial biofilm formation in foods as well as for food bio-preservation (Motalebi Moghanjougi et al. 2020; Silva et al. 2018). The idea behind the postbiotics covers the microbial fragments and their metabolites that have a positive impact on the host. Due to different architectural and heterogeneity, a variety of possible acquisition methods is implied by the postbiotics. Bacterial cells can be lysed by mechanical or chemical means. These techniques include heat, sonication, solvent extraction, and enzyme extraction. To seggregate and recognize desired compounds, chromatography, dialysis, and extraction are employed (Fiore et al. 2020; Wegh et al. 2019). The current research investigates the formation of postbiotic metabolites in food, in situ, as well as the effects of both the external and the internal components of food. In addition to this, the antibacterial roles, the elimination of biofilms, and all of its uses in food standards and storage have been considered. This review, however, was meant to focus on the very recent uses of postbiotics to ensure food safety. The possible usage of postbiotics in food packaging, food biopreservation and preventing and getting rid of biofilm that comes from food were looked at. This study also investigated a variety of other topics, such as the combination of postbiotic composition in the food system and the precautions that should be taken with regard to it.

Production of postbiotics

The food that is most frequently used to provide probiotics is yoghurt. Numerous products, both fermented (like yoghurt and cheese) and non-fermented (such as cereal and chocolate bars), have probiotics added to them. Certain food characteristics, such as acidity, water activity, specific chemical components, moisture, temperature, package permeability to oxygen, and duration, can pose challenges for probiotics in terms of survival during both production and storage. Most of the stated health advantages of fermented milk have been verified. Another example of a food that provides probiotics, prebiotics, symbiotics, and postbiotics is infant formula (Aguilar-Toalá et al. 2018; Damián et al. 2022). Fermented infant formula has been made specifically using *Bifidobacterium breve* and *Streptococcus thermophilus*. The bacteria are then killed by spray drying following the fermentation process. Inanimate bacteria and fermentation byproducts are present in the newborn formula. A number of pediatric clinical studies showed its safety and postbiotic properties, including modulating the gut microbes to be more similar to that of infants under breastfeeding, reducing the grievousness of severe diarrhea, improving immune markers and inflammatory, which may be

connected to few attributes of the gastrointestinal tolerance, and reducing digestive symptoms. Apart from the above, it reduces allergic reactions in babies, as well as the prevention of thymus enlargement and alkaline stools in healthy-term infants (Chaluvadi et al. 2015; Cristofori et al. 2021; Maguire & Maguire 2019). Food supplements are a viable sector for the creation of new postbiotic products since they may have longer shelf lives than probiotic food supplements due to their lack of viability. The range of microorganisms used for functional purposes will probably expand as a result of the idea of postbiotics. Species beyond those from the usually benign genus Bifidobacterium or the family Lactobacillaceae, that were unable to be managed live due to safety and health issues, have been examined as potential postbiotics (Chang et al. 2021; Foo et al. 2019; Liu et al. 2020). Postbiotics can be included in foods and ingredients prior to heat processing without impairing their functions because they are stable throughout a wide range of temperatures. Producers might benefit from this in terms of technology and finances. Postbiotics can be employed in drug carriers such as food supplements and/or pharmacological items since their correct dose can be managed during manufacturing and storing parameters when survivability is not the key deciding factor (Wegh et al. 2019). The production of postbiotics involves several techniques, including sonication, enzymatic treatments, and chemical processes. These methods play a crucial role in extracting bioactive components, modifying microbial structures, and ensuring the viability and effectiveness of postbiotics for various health-promoting applications. The choice of method for postbiotic production depends on various factors, including the desired postbiotic compound, the microbial strain used, the intended application, and scalability considerations. Researchers and manufacturers carefully select the most suitable method to maximize the yield, quality, and safety of postbiotic products. Production of postbiotics through various techniques has been illustrated in Fig. 3.

The most common postbiotic source in the food sector is fermentation. Many milk-based products, as well as other items including kefir, kombucha, yoghurt, and pickled vegetables, naturally contain postbiotics. The producer strains, which can be utilized to extract the postbiotics in situ, primarily consist of *Lactobacillus* and *Bifidobacterium* strains, but they may also contain *Streptococcus*, *Akkermansiamuciniphila*, *Eubacteriumhallii*, *Faecalibacterium*, and *Saccharomyces boulardii* (Gezginç Et Al. 2022; Hernández-Granados & Franco-Robles 2020; Żółkiewicz et al. 2020). A variety of bacteriocins have also been discovered, described, and may have future industrial applications. The microbiological strains and growth parameters will influence their extraction and characterisation. Nisin, also used as a preservative substance in numerous food products (canned soups, dairy products, infant formula), can be made by *Lactococcus lactis*, however they must first be physiologically inert before being transformed to become active (Basavanna & Prapulla 2013). A number of research have also concentrated on using enzymes rather than probiotic bacteria

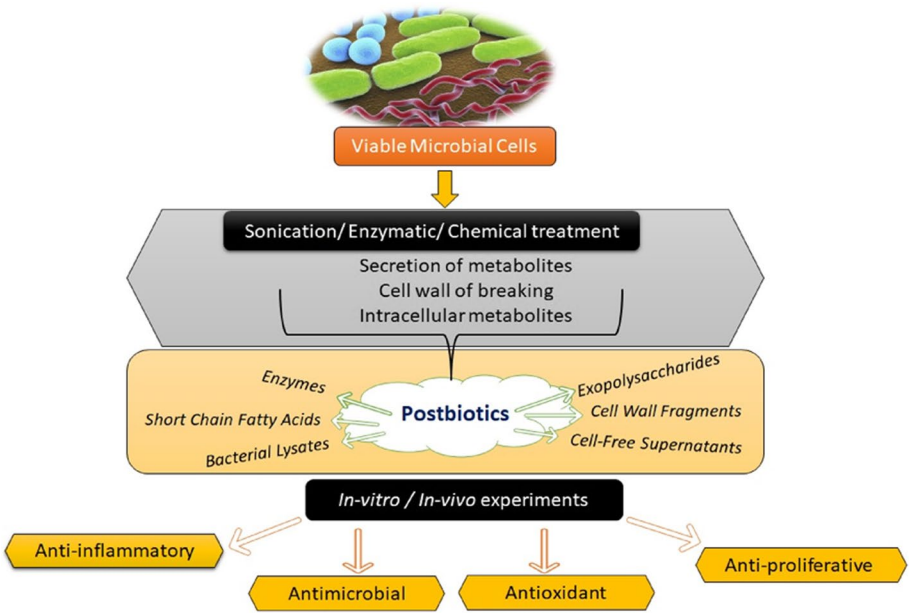


Fig. 3 Schematic representation for production of postbiotics through various techniques and its bioactivities

to produce particular results. *Bifidobacterium pseudocatenulatum* and *Bifidobacterium longum* producing postbiotic enzymes like purified phytases, for instance, increased myoinositol triphosphate levels while reducing the amount of phytates in cereal combinations. Numerous writers have also reported vitamin enrichment in food products. It's a very frequent practice to use fermentation to increase vitamin B content in cereal grains. Vitamin B is abundant in cereal grains. These vitamins, however, are lost during grinding or heat processing. The number of bacteria which can create the vitamins B1, B2, B3, B9, B11, and B12 is increased by cereal fermentation and LAB (Lactic Acid Bacteria) pre-treatment. The LAB fermentation of cereals consequentially enhanced the amounts of protein fractions, total lysine, soluble dietary fiber, sugars and Fe, Ca, and Zn bioavailability in vitro. Additionally, wheat could yield antioxidant peptides, -aminobutyric acid, and angiotensin I-converting enzyme-inhibitory peptides through LAB fermentation (Khalil et al. 2018; Kumar et al. 2017; Masuda et al. 2012).

Postbiotic and food additive interactions

Impact of nutritional factors on postbiotic

The performance of postbiotics is influenced by both internal (matrix substances: food composition, pH levels, moisture content) and external (all elements affecting the storage of food: temperature, oxygen exposure, light exposure, time and duration, packaging materials) factors of food (Patil et al. 2019). The findings of the studies have demonstrated that these variables have a major impact on the structure, nature, and functions of postbiotics, that is important when evaluating the ideal circumstances for their manufacture and use in pharmaceutical or food products (Rad et al. 2021).

Internal factors

The function of postbiotics can be impacted by a variety of food additives like preservatives, emulsifiers and stabilizers, sweeteners, colorants and flavors, and antioxidant etc. The function of metabolites can be inhibited by interactions between active postbiotic metabolites and specific food components such enzymes, proteins, carbs, endogenous microflora, and lipids (Rad et al. 2021). As an illustration, food-borne proteolytic enzymes may influence the activity of postbiotic substances (Peluzio et al. 2021). In order to prevent postbiotic protein molecules from functioning, proteolytic enzymes can degrade them. Either the feed itself contains these enzymes or the proteolytic bacteria in the diet produce them. Trypsin, chymotrypsin, pepsin, papain, and proteinase K are the most crucial enzymes (Abdulhussain Kareem & Razavi 2020). The protease enzyme, for instance, breaks down the protein when proteinaceous postbiotics are used, preventing the postbiotic action. Proteolytic enzymes should therefore be taken into account when talking about postbiotic dysfunctions. Fermented dairy products (e.g., Yogurt and Kefir), fermented vegetables (e.g., Sauerkraut and Kimchi), fermented soy products (e.g., Miso and Tempeh), fermented grain products (e.g., Sourdough Bread) are the examples of foods where enzymatic activity can indirectly promote a favorable environment for postbiotic production. However, there are no examples of postbiotic combinations with dietary components having synergistic or antagonistic effect (Nataraj et al. 2020).

External factors

The antibacterial action of postbiotics can be impacted by food pH. Foods that are acidic or alkaline can make postbiotics less effective (Ebrahimi et al. 2021). Postbiotic activity has a specific range of application. The ideal pH range for postbiotic action is between 4 and 9 (Prabhurajeshwar & Chandrakanth 2017). Pasteurized milk and ground beef were few of the food components which used postbiotics to manage microorganisms because they had good pH levels and no postbiotic function disturbances. Another external element that may have an impact on postbiotic performance is heat. Postbiotics' ability to fight against microbes can be hampered by heat. Postbiotic chemicals' antibacterial action is diminished for 30 min at 30 °C and then for 15 min at 121 °C (Chelliah et al. 2016). As a result, food heating can also have a big impact on the activity of postbiotics. In this instance, maintaining the temperature parameter at an ideal level, is very crucial (Pavli et al. 2018).

Different classes of postbiotics and its bioactivities

The postbiotics can be classified based upon its chemical nature and its bioactivities. Various types of postbiotics and its role in food preservation have been discussed in this section. A synopsis of the few studies that have been reported on postbiotics and their use in a variety of food products has been describes in Table 1.

Organic acids

Inhibiting food spoilage bacteria is one among the most significant effects induced of postbiotics in the food sector. Compounds suitable for use as antibacterial agents include organic acids. One of the important postbiotics is recognized to be organic acids. Two isomers of lactic acid, L and D, which are formed by bacterial fermentation processes, efficiently limit pathogenicity. Additionally, by generating an acidic environment, acids like acetic acid and citric acid prevent the formation of infections. Acetic acids (pka = 4.76) and Lactic acids (pka = 3.86) among organic acids prevent the growth of infections by lowering pH levels in in vivo or/and in vitro condition. Organic

Table 1 Summary of few reported studies in postbiotics and their applications in different food products

S.L No	Name of the food	Postbiotic element	Source organism	Key finding	References
1	Yoghurts	Polysaccharide	*Lactariusvolemus*	Increased water absorption and pH reduction	(Huang et al. 2020)
2	Soybeans	Extracellular products	*Lactobacillus plantarum* YML 007	Shelf life has been extended to two months	(Rather et al. 2014)
3	Cheddar cheese	Exopolysaccharide	*Lactobacillus rhamnosus*	enhanced product functionality	(Torino et al. 2015)
4	Cereal mixtures	Purified physates	*Bifidobacterium longum*, *Bifidobacterium pseudocatenulatum*	Decreased physate concentration and raised myo-inositol triphosphate levels	(Tamayo-Ramos et al. 2012)
5	Cheddar cheese	Unknown enzyme	*Lactobacillus rhamnosus* S93	Increased levels of soluble nitrogen in phosphotungstatic acid and free amino acids	(Azarnia et al. 2010)
6	Grilled beef	Extracellular products	*Lactobacillus sakei* NRRL B-1917	Decreased number of *Listeria monocytogenes* and *E. coli*	(Beristain-Bauza et al. 2017)
7	Custard cream	Bacteriocin	*Lactobacillus gasseri* LA39	Four decomposition strains are completely inhibited	(Nakamura et al. 2013)
8	Food in general	Bacteriocin	*Lactobacillus coryniformis* MXJ 32	Bactericide for *Staphylococcus aureus* and *Escherichia coli*	(Lü et al. 2014)
9	Chicken breast	inhibitor Substance like- Bacteriocin	*Lactobacillus plantarum* ST16Pa	Bioconservative against *Enterococcus faecium* for 7 days	(Da Silva Sabo et al. 2017)
10	Ground beef and whole milk	Pirrolo [1,2-a] and pyrazine-1,4-dione	*Lactobacillus salivarius*	Biofilm removal of *Listeria monocytogenes*	(Moradi et al. 2019)
11	Kombucha Tea	Polyphenols	*Acetic acid bacteria and yeast*	Improved antioxidant properties and anti-inflammatory effects	(Jayabalan et al. 2014)
12	Kimchi	Lactic acid Bacteria Metabolites	*Lactobacillus plantarum and Lactobacillus brevis*	Enhanced gut health and immune modulation	(Jung et al. 2011)
13	Miso soup	Peptidoglycans and Teichoic Acids	*Saccharomyces cerevisiae and Lactobacillus sakei*	Regulation of gut microbiota and anti-inflammatory effects	(Fukuda et al. 2011)
14	Fermented pickles	Organic Acids (e.g., Lactic Acid)	*Lactobacillus plantarum and Pediococcus pentosaceus*	Improved digestion and nutrient absorption	(Marco et al. 2017)
15	Tempeh	Oligosaccharides and Peptides	*Rhizopus oligosporus*	Prebiotic effects, promoting the growth of beneficial gut bacteria	(Ahnan-Winarno et al. 2021)
16	Natto	Nattokinase (Fibrinolytic Enzyme)	*Bacillus subtilis* var. *natto*	Cardiovascular health improvement and blood clot prevention	(Chen et al. 2018)
17	Fermented Dairy products	Bacteriocins and Organic Acids	Various Lactic Acid Bacteria Strains	Enhanced shelf life and inhibition of harmful bacteria	(Guillemard et al. 2010)
18	Sourdough Bread	Lactic Acid and Phenolic Compounds	*Lactobacillus sanfranciscensis and Candida milleri*	Reduced gluten content and improved digestibility for gluten-sensitive individuals	(Papadimitriou et al. 2019)
19	Sauerkraut	Glucosinolates and Isothiocyanates	*Lactic Acid Bacteria*	Anticancer properties and immune system support	(Vitali et al. 2012)
20	Fermented Fish Sauce	Amino Acids and Peptides	Various Marine Bacteria and Yeasts	Rich source of umami flavor and potential antimicrobial effects	(Faisal et al. 2015)

Table 1 (continued)

S.L No	Name of the food	Postbiotic element	Source organism	Key finding	References
21	Kimchi	Bioactive soluble byproducts	*Leuconostoc mesenteroides J.27*	*Leu. mesenteroides* (LAB J.27) and food-grade EO (eugenol or thymol) was highly effective against a variety of pathogenic bacteria	(Toushik et al. 2022)
22	Frankfurters	Bacteriocin	*Pediococcus acidilactici*	Antimicrobial effect against *Escherichia coli, Salmonella*, *Typhimurium*, *Listeria monocytogenes* on frankfurters during refrigerated storage	(İncili et al. 2022)
23	Korean kimchi	Biopreservative	*Lb. plantarum YML 007*	Cell free supernatant improved shel life of unshelled soybeans upto 2 months	(Malashree et al. 2019)
24	Baker's yeast	vitamins, polyphenols, sterols, and phospholipids	*Saccharomyces cerevisiae*	EpiCor is an immunogen product	(Bourebaba et al. 2022; Jensen et al. 2007)
25	Traditional koumiss	Whole peptidoglycan (WPG)	*Lactobacillus paracasei* sub sp. *paracasei* M5 strain	Potential anticancer activity	(Bourebaba et al. 2022; S. Wang et al. 2018a, b)
26	Breast-milk feeding	Lipoteichoic acid (LTA)	*B. animalis* subsp. *lactis* CECT 8145	Reduces fat deposition	(Balaguer et al. 2022)
27	Yogurt	D-alanyl-lipoteichoic acid	*Lactobacillus plantarum* CRL1506	Modulate the Intestinal Antiviral Innate Immunity	(Mizuno et al. 2020)
28	Tomato processing waste	Exopolysaccharides	*Lactobacillus buchneri* TCP016	Induced liver injury and improves the modification of the gut microbiota	(Xu et al. 2019)
29	Fermented Fuyuan pickle	Exopolysaccharides	*L. fermentum* S1	Promising functional adjunct for application in foods	(Wang et al. 2020)

acids' impact on bacterial cell membranes is connected to their inhibitory action. Decreasing the pH inside the cell and maintaining membrane integrity are the key mechanisms at play here (Chang et al. 2021). There are two connections between organic acids' antibacterial properties preventing or regulating acidification of cellular cytoplasm and energy production. Organic acids (tartaric acid, acetic acid, lactic acid, citric acid, and malic acid) produced by three strains of *Lactobacillus plantarum* (P1, S11, and M7) and looked into how effective these acids were at killing pathogenic bacteria (*Escherichia coli* and *Salmonella*) (Hu et al. 2019). They discovered that *L. plantarum* strains reduce the growth of harmful bacteria by secreting organic acids. Organic acids work to kill bacteria by bringing down their pH and acidifying their cell membranes. Lactic acid and acetic acid are two organic acids that have particularly potent antibacterial properties. These findings suggest that a strategy involving the mixing of various organic acids could be used to generate new antibacterial agents for widespread usage in the food industry (Chelliah et al. 2016; Ebrahimi et al. 2021; Moradi et al. 2021; Patil et al. 2019; Pavli et al. 2018; Peluzio et al. 2021; Prabhurajeshwar & Chandrakanth 2017).

Bacteriocin

Antimicrobial peptides or proteins known as bacteriocins are produced by a variety of bacteria, including *Archaebacteria* and *Eubacteria*. Because of their potent antibacterial properties, bacteriocins have been utilized by humans in fermented meals for countless years. Bacteriocins are classified according to their size, mode of action, and spectrum of inhibitory activity. Bacteriocins offer a variety of advantageous properties, such as the ability to withstand heat and pH changes and to inhibit the development and growth of gastrointestinal infections. The inhibition of spore formation, pore development on pathogenic cell membranes, and impacts on the morphological and functional properties of bacterial peptides are all key components of bacteriocins' antibacterial mechanism (Abdulhussain Kareem and Razavi 2020; Kim et al. 2020). Wang et al. (2018a, b) employed fish-isolated *Lactobacillus plantarum* LPL-1 bacteriocins against *Listeria monocytogenes* in a study (Wang et al. 2018a, b). It

was discovered as a result that the bacteriocins might stop *L. monocytogenes* from growing by acidifying its cell membrane and producing pores in the bacterial membrane. Kim et al. (2020) and his colleagues examined the effectiveness of *Lactobacillus taiwanensis* produced bacteriocins against *Escherichia coli* and *Salmonella gallinarum* in a different investigation. As a result, it was discovered that *L. taiwanensis* bacteriocin may destroy pathogenic bacteria's protein structures and impede bacterial development by lysing their membranes. Bacteriocins can be utilized as a technique to reduce the bacteria that can cause food spoiling, according to the findings of the studies listed above (Kim et al. 2020).

Fatty acids

Antibiotics can be replaced with fatty acids and their derivatives. For over a century, it has been recognized that fatty acids possess antibacterial properties. Fatty acids are generated by joining a hydrophilic carboxylic group to a saturated or unsaturated carbon chain. Additionally acknowledged as possible postbiotics with significant antibacterial effects are fatty acids (Patil et al. 2019). Eicosapentaenoic acid (EPA), a long-chain fatty acid, inhibits the growth of Gram-positive bacteria. Lauric and meristic acids, among other fatty acids, have a strong inhibitory effect on the growth and development of microorganisms. Fatty acids have antimicrobial effects on bacteria by causing cell lysis, increased membrane permeability, disruption of the electron transport chain, disruption of enzyme activity and structure, and induction of functional/ morphological alterations in sensible components like proteins. The impact generated by fatty acids induced by *L. fermentum*, *Lactobacillus acidophilus* and *L. paracasei* against *Klebsiella oxytoca* was investigated by Higashi and colleagues in 2020. They discovered that the probiotic bacteria's fatty acids lyse *Klebsiella oxytoca*'s cell wall, preventing *Klebsiella oxytoca* from growing (Higashi et al. 2020).

Peptides

Antimicrobial peptides are produced by microorganisms. Peptides kill microorganisms by inhibiting the synthesis of macromolecules and degrading microbial membranes, which is known as pleiotropic processes. There are two categories of antimicrobial peptides: ribosomal and non-ribosomal. The bacteria's ribosomal proteins exhibit potent antibacterial action in vitro by rupturing microbial membranes. Nearly all bacteria have peptides. As was already noted, some peptides primarily target cell membrane, whereas others target cytoplasm and delicate bacterial structures. The peptides' antimicrobial effects include (a) causing the bacterial cell membrane to become acidic, (b) producing physical holes that allow cells to leak out, (c) generating hydrolases that harm the cell wall, and (d) harming the microorganisms' sensitive internal components. *E. coli* Nissle 1917 peptides were used by Forkus et al. (2017) to combat *Salmonella enterica* that was isolated from digestive system of the turkey. In this work, it was discovered that *Salmonella enterica* growth is inhibited by *E. coli* Nissle 1917 antmicrobial peptides that damage the cell wall. *Bacillus subtilis* produces antibacterial peptides that have been tested for effectiveness against *E. coli* and *L. monocytogenes*. According to the study, *Bacillus subtilis* peptides harm sensitive structures in order to prevent germs from growing. These findings raise the possibility of employing probiotic-produced antimicrobial peptides for food preservation (Forkus et al. 2017; Osés et al. 2015).

Unlike ribosomal peptides, non-ribosomal peptides are produced through non-ribosomal peptide synthetases (NRPS) or polyketide synthases (PKS), complex enzyme systems that are capable of assembling peptides from individual amino acid building blocks. These non-ribosomal peptides can have diverse structures and functions (Enzyme inhibition, immune modulation, and biofilm disruption etc.) including antimicrobial activity (Hernández-Granados and Franco-Robles 2020; Li et al. 2021).

Hydroxyl radicals

H_2O_2 can be converted into hydroxyl radicals, which have potent oxidative properties. All bacteria primarily create hydrogen peroxide, which is the principal metabolite of lactic acid bacteria and is typically found in catalase-negative bacteria under aerobic culture. The inhibitory and antibacterial effects are primarily determined by the concentration of hydrogen peroxide (H_2O_2), which can have variable effects depending on a number of factors. Bacterial concentration can also be influenced by a number of variables, including particular bacterial strains and ambient conditions (temperature and pH). H_2O_2 has powerful oxidizing properties that cause damage to cytoplasmic protein structures in bacteria, which contributes to its antibacterial activities (Li et al. 2021; Markowiak & Ślizewska 2017). The effectiveness of *Bifidobacterium longum, B. infantis, Lactobacillus acidophilus*, and *L. rhamnosus* breve against methicillin-resistant *Staphylococcus aureus* (MRSA) in vitro was examined. The research found that hydrogen peroxide produced by probiotic bacteria can reduce the growth of Staphylococcus aureus. According to these findings, postbiotic substances like hydrogen peroxide can be utilized as an effective substitute for antibiotics in the fight against pathogens and spoilage of food (Żółkiewicz et al. 2020).

Vitamins

Large amounts of vitamins are produced by probiotic bacteria in the food matrix and the stomach of the host. Although probiotic bacteria in the colon produce very little vitamin material, food matrix production of vitamins, particularly in dairy products, greatly rises. It was discovered through researching the probiotic bacteria's antibacterial function that the vitamins these bacteria produce are crucial in blocking dangerous germs. Vitamin compounds are created in lab models by breaking down probiotic microorganisms (*Lactobacillus plantarum*). Comparatively, vitamin C plays a stronger antibacterial role. Vitamin C raises the acidity of the lipids in bacterial cell membranes, causing the membrane and cell wall of the bacteria to be lysed. Postbiotic chemicals have valuable antibacterial capabilities, and the food industry can utilize these compounds in a variety of ways to preserve food and lengthen food shelf (Cueva et al. 2010; Górska et al. 2019).

Applications of postbiotics in food biotechnology

Because microbiological deterioration, notably mould growth, starts on the food's surface, it is not practical to cheaply embed a significant amount of the preservative in the matrix of the food because this would result in the food becoming contaminated (Vilela et al. 2018). Use of food packaging to increase food's shelf life has been suggested as a potential solution to these issues.

Bio preservation of food

Dairy products have been used in the past to help the good bacteria in the stomach (probiotics). Probiotic strains might not survive during processing and storage, nevertheless, if extrinsic elements that cause dairy components to degrade have an adverse effect. Including postbiotics in dairy products is a cutting-edge method of enhancing their safety. The preservation of food naturally depends on postbiotic performance characteristics. From a safety standpoint, producing postbiotic compounds in a Mannitol Salt Agar Culture medium is less thrilling than manufacturing postbiotics. For instance, Mehran Moradi et al. researches demonstrated that postbiotics prepared by MRS may show considerable detriment on the product's sensory qualities and affect total customer acceptability. Milk is a substance that can absorb substances that change its colour and consistency because of its whiteness, fluidity, and opacity. In a recent study, postbiotics generated from three probiotic milk strains were assessed as antifungal drugs to inhibit the development of mould in semi-hard cheese and sour cream. Postbiotics were discovered to drastically lower the number of fungi in cheese while possibly having no negative effects on sensory perception. As a spray-form antibacterial agent to prevent dangerous germs, postbiotics have recently been proposed (Moradi et al. 2019).

Multiple studies have shown that postbiotic components are effective in improving the preservation of refrigerated meat. For instance, in a recent study, *Bifidobacterium lactis* Bb-12 is directly added to minced meat, which extended its preservation for up to three months at 4 °C (68). Similarly, *Lactobacillus rhamnosus* EMCC 1105 postbiotics at a concentration of 100 mg/g eliminated *Clostridium perfringens* in minced chicken after four days of storage at 6 °C. The antibacterial action of postbiotic molecules is determined by their type, with bacteriocins being potent antibacterial agents (69). In one study, postbiotics from three probiotics (*Lactobacillus casei* 431, *Lactobacillus acidophilus* LA5, and *Lactobacillus salivarius*) were evaluated for their antibacterial effects on *Listeria monocytogenes* in minced beef and Luria Bertani broth. The postbiotic substance inhibited *L. monocytogenes* and prevented the deterioration of Luria Bertani broth and minced meat (70).

Removal of biofilm

There are a variety of microorganisms with varying rates of growth that may include one or more different types. In a protein or carbohydrate matrix, a complex microbial population is called a biofilm. Microorganisms like bacteria and fungi can generate biofilms (Urish et al. 2016). These abilities are shared by gram-negative and gram-positive bacteria. One of the major problems facing the world today is the bacterial resistance to antimicrobials during the biofilm phase. Reversible and irreversible surface adhesion, microclone forms with exopolysaccharide synthesis, and other production steps are among them. For the food product industry to make ensure food safety, controlling colony components and irreversible biofilms is crucial. The removal of biofilms created by the food industry is less effective when cleaning and disinfecting surfaces (Andrade et al. 2020; Przekwas et al. 2020). Some major bacteria that create biofilms are *Campylobacter jejuni*, *Yersinia enterocolitica Listeria monocytogenes* and *Staphylococcus aureus*. To manage and eliminate bacterial biofilms, a variety of techniques have been employed. An innovative method for removing biofilms is to use postbiotics. It has been found in recent studies that postbiotics can successfully remove bacterial biofilms (Andrade et al. 2020; Przekwas et al. 2020. In a study, probiotic bacteria *Lactobacillus casei* 431, *Lactobacillus acidophilus* LA5, and *Lactobacillus salivarius* were used to cure a biofilm created on polystyrene surfaces by *L. monocytogenes*. It has been discovered that postbiotics inhibit the growth of biofilm. The authors illustrated that the lack of postbiotics containing bacteriocin and organic acids was the primary factor in reducing the biofilm of

L. monocytogenes. Postbiotics are a viable strategy in the food product industry to prevent the development of bacterial biofilm (Sharma et al. 2018; Shi & Zhu 2009).

Development of active food packaging

As consumer preferences and market trends change, one of the most inventive methods of food packaging is called "active packaging" (Ahmed et al. 2017). The primary active packaging strategies target flavours, odours, antimicrobials, antioxidants, moisture, ethylene, carbon dioxide, and those that release CO_2. The shelf life of food is affected by a combination of parameters, includes the food product itself, the packaging material used, and various environmental conditions. An active packaging system known as "antimicrobial active packaging" protects food from microbial decomposition during transportation and storage by adding antimicrobial agents (AAs) of plant, animal, and microbial origin or their metabolites, antimicrobial nanoparticles, etc., in the packaging (Yildirim et al. 2018). Due to various environmental factors that can affect the survival of probiotics in bioactive packaging and the production of antimicrobial substances, such as temperature, relative humidity, light intensity, and amount of moisture in food, the antimicrobial efficacy cannot be accurately predicted. Moreover, the consumption of bacterial cells can alter the thermal, barrier and mechanical characteristics of the packaging material. Because of these aspects, antimicrobial packaging methods (use live bacteria) can use postbiotics.

Application of individual postbiotics

The use of postbiotics produced by various probiotic strains is also possible for food-active packaging. Bacteriocins, bioactive peptides have antibacterial properties, are the most often employed postbiotic metabolites in the food sector (Mohammadi et al. 2022). The development and assessment of bacteriocin-loaded active packaging devices is of great interest to many researchers for the aforementioned reasons. Despite the fact that there are a multitude of bacteriocins, nisin is the one that is very well-known and regularly utilized in the production of antimicrobial drug films. Several different strains of the bacterium *L. lactis* produce it (Silva et al. 2018). The effectiveness of starch halloysite nanocomposite films loaded with pediocin and nisin in inhibiting *Clostridium perfringens* and *Listeria monocytogenes* was assessed for their antimicrobial activity. The findings revealed that while pediocin and nisin had varying degrees of antilisterial activity, nisin had higher levels of antagonistic activity against *Clostridium perfringens*. Furthermore, the presence of halloysite aided in reducing bacteriocin diffusion and improved antimicrobial agent retention in the polymer matrix (Meira et al. 2017).

Another type of isolated individual postbiotic used in the production of antimicrobial films is enterocin, which is produced by various *Enterococcus* species. To create the films mentioned in (Ibarguren et al. 2015), enterocin A, B, and P were combined with gelatin. This demonstrates that. The film loaded with enterocin was effective in inhibiting Listeria monocytogenes, *Staphylococcus aureus,* and *Bacillus cereus*. Furthermore, when both prunin laurate and enterocines were incorporated into the film simultaneously, a synergistic inhibitory effect was observed against these microorganisms. They further noted that the addition of active compounds had no impact on the gelatin films' mechanical, thermal, or barrier properties. Bacteriocins are popular and widely used, but they have a significant drawback that prevents them from being used in all situations: they are expensive to produce and have a low yield.

Application of postbiotics mixture

The solution of postbiotics comprises several physiologically active metabolites that exhibit synergistic antibacterial properties towards both the food products and films (Bali et al. 2016). A suitable antimicrobial agent is postbiotics, and interest in creating antimicrobial agent-infused movies has grown recently. *Lacticaseibacillus rhamnosus* NRRL B-442 (6, 12 or 18 mg/ml) and calcium caseinate films were used in an experiment. The results of their investigation suggested that postbiotics applied at a conc. of 18 mg/mL had antimicrobial activity (Beristain-Bauza et al. 2016). *Staphylococcus aureus*, *E. coli*, *Listeria monocytogenes*, and *Salmonella typhimurium* have all been successfully tested in both movies without having their physical characteristics changed. Postbiotics were added to brown ink coatings, which resulted in coatings with lessened puncture resistance and moisture vapor transport (Beristain-Bauza et al. 2016). Whey protein isolate alginate films were created by and coated with postbiotics from *Lactobacillus Sakei* NRRL B-1917 for the purpose of packaging beef cubes contaminated with *Listeria monocytogenes* or *E. coli*. Following 120 and 36 h of cooling, *Listeria monocytogenes* and *E. coli* displayed corresponding decreases in CFU/g of 1.4 and 2.3 $\log_{10}$. The findings indicated that there were no notable distinctions between the grilled beef samples that underwent packaging and those that did not undergo any packaging at all (Beristain-Bauza et al. 2017).

Through the use of bacterial nanocellulose and postbiotics from *Lactiplantibacillus plantarum*, an antibacterial meat wrap nanopape was created in an experiment (Shafipour Yordshahi et al. 2020). A network with less porosity was produced as a result of the immobilisation of postbiotics on the nanocellulose matrix. It was possible to produce films with strong antimicrobial activity

using postbiotics, but doing so might compromise the films' physico-chemical characteristics. Postbiotics must therefore be applied at a concentration that maximizes both their thermomechanical and antibacterial propertiesput forth the hypothesis that the improved storage stability of bacteriocins brought about by their immobilisation on cellulose nanocrystals counteracts the negative effects of postbiotics on the barrier and mechanical properties of starch films (Bagde & Nadanathangam 2019).

Manipulation of postbiotic composition in food

The majority of postbiotic sources in the food industry are obtained through the process of fermentation. Postbiotics are naturally occurring microorganisms that can be found in many dairy products, as well as in kefir, kombucha, yoghurt, and pickled vegetables. The extracellular biopolymers, or EPS, that bacteria produce or exude as they develop. The sensory and physiochemical qualities of products made from food can be improved by EPS produced by LAB, including *Lactobacillus rhamnosus*, a crucial component in dairy products (Nguyen et al. 2020). Numerous research have centered the use of enzymes rather than probiotic microorganisms to achieve desired results. For instance, purified phytases derived from Bifidobacterium longum and *Bifidobacterium pseudocatenulatum* have been found to increase myoinositol triphosphate levels and decrease phytate levels in cereal blends. Food items are supposedly vitamin-enriched, according to numerous authors. It's not unusual to use fermentation to increase the vitamin B content of cereal grains. Vitamin B is abundant in grains used for cereal. These vitamins are lost, though, during grinding or heat processing. Fermenting cereal and pre-treating it with LAB (lactic acid bacteria) can result in producing additional bacteria that are capable of synthesizing vitamins B1, B2, B3, B9, B11, and B12. (Nkhata et al. 2018). The LAB fermentation of cereals significantly improved the Ca, Fe, and Zn's *in-vitro* bioavailability as well as sugars, soluble dietary fiber, total lysine, and protein fractions. Through LAB fermentation, wheat may also generate aminobutyric acid, peptides that protect against oxidation, and peptides that block the angiotensin I-converting enzyme. Using probiotic-induced fermentation to eliminate some potentially harmful food components is another creative way to use probiotics in addition to adding postbiotics to food (Bai et al. 2021).

Safety concerns and future prospects

Numerous studies have offered convincing proof of the advantages of bacteria, especially in the gut. In light of the possible risks and safety concerns, the regulatory requirements for postbiotics and other similar functional meals should be anticipated. Despite the risks associated with foodborne bacteria that have already been mentioned, LAB (lactic acid bacteria) and bifidobacteria, which are considered to be beneficial bacteria, can effectively compete against pathogens and release amino acids (AAs) that enhance the lifespan and safety of food products (Nataraj et al. 2020). Additionally, these bacteria have the power to act as potent barriers to the emergence of pathogens and spoilage-causing microbes. The limitations of probiotics led to the development of the postbiotic idea, a novel approach for functional food ingredients. On the other hand, it might be necessary to take into account the probiotic strains, the type of fermentation, and the safety concerns for consuming postbiotics when producing postbiotics (Anderson 2019; Żółkiewicz et al. 2020). Despite the fact that postbiotic eating is still a new strategy, there is no epidemiological or clinical proof of any dangers. The threat of infection is ostensibly gone, though, because there are no active microbes. Studies in vivo and in vitro investigated how postbiotics affected various cell types, blood parameters, metabolic markers, and intestinal mucosa. In vitro research is expected to be advantageous for studying how commensal and pathogenic microbes interact with the host along with its microbial products. In vivo studies are highly encouraged to confirm the effects of postbiotics in *in-vitro* due to the limited transferability of in vitro research and the possibility of species-specific effects. Numerous animal models for postbiotics, short chain fatty acids, peptides, EPS, vitamins, peptidoglycans, lipopolysaccharides, teichoic acids, and peptidoglycans have all been identified as potential alternative treatments for infectious diseases in the aquaculture system (Nataraj et al. 2020).

The role of the intestinal epithelial barrier as the primary defense mechanism against numerous infections is widely recognized. As a result, leaky gut, also known as a disruption in the gut epithelium barrier's regular operation, can allow a variety of harmful substances and organisms to enter the body. Postbiotics are therefore potential options since any drugs that have the ability to improvise the intestinal barrier can be recognized as health-promoters. Not only do living bacteria in the digestive tract benefit from fermented foods, but so do other beneficial organisms. The byproducts of fermentation may also have positive health effects. Postbiotics maintain host health and may act as a mediator for the positive effects via a number of pathways, but the targeted mode of action is still under study. The use of postbiotics in the right amounts and concentrations has been proven to be safe by a number of studies. Food safety is improved by postbiotics' antibacterial properties. Some of the elements that determine the antibacterial effect of postbiotics inside the foodservice industry include the kind and dosage of postbiotics, the type of food modeling, and the

features of the food product. The management of food-infecting bacteria is one of the most significant effects of postbiotics on the food industry (Anderson 2019; Dimidi et al. 2019).

Experts predict that postbiotics will have an effect on how the human body works and offer a fascinating area for future study. New products are being introduced by manufacturers to meet the demands of various customers as the research sector grows. Postbiotics provide an advanced and secure way to supplementally improve gut health because they have fewer storage and shelf-life issues than live probiotics. The potential for meals and beverages based on postbiotics has grown as a result of rising health concerns and the subsequent trend toward functional foods. People understand how important their gut microbiota is and how it affects their overall health. Microbial metabolites have come under scrutiny due to the technological challenges posed by the presence of viable microbial cultures in various foods and beverages, as well as the possibility that they could harm immunocompromised people. The demand for healthier food choices by consumers has caused significant transformations in the food and beverage industries. The market is demonstrating that there is a chance for businesses to include postbiotics in the formulations of their products in order to appeal to more customers (Collado et al. 2019; Salminen et al. 2021b). Not only do postbiotics have many health advantages, but they also serve as emulsifiers, preservatives, and guarantee the stability of the finished product, thereby lowering the need for food additives. Researchers are still attempting to determine how postbiotic production may affect people's health, and there aren't many studies on the advantages of postbiotics. In the majority of recent studies, dietary supplements are compared to pre- and probiotic meal consumption (Aguilar-Toalá et al. 2018; Damián et al. 2022).

Conclusion

In summary, the growing interest with functional foods, including probiotics, prebiotics, and postbiotics, has garnered substantial interest from consumers, manufacturers, and researchers in recent years. Postbiotic dietary supplements are notable for their superior stability in comparison to probiotics and prebiotics, rendering them very promising contenders for diverse applications, particularly in the domains of food safety and preservation across the food chain. The objective of this study, as indicated in the passage, is to offer a thorough examination of postbiotics, encompassing their capacity to enhance health, methods of production, nomenclature, biological activities, and their uses in ensuring food safety and preservation. Postbiotics have been observed to exhibit their efficacy in the field of bio preservation by effectively mitigating the formation of biofilms in food products through the use of organic acids, bacteriocins, and several other antibacterial mechanisms. Moreover, the research investigates the in-situ synthesis of postbiotic metabolites in food and examines the impact of both external and internal food constituents on this phenomenon. This study investigates the antibacterial characteristics of postbiotics and their potential utilization in the preservation of food items, hence leading to an overall improvement in food safety.In general, this study on postbiotics presents a potentially fruitful direction for advancement in the food industry. It presents potential solutions that are in line with consumer preferences for healthier, safer, and more sustainable food products. Additionally, it addresses the intricate challenges associated with food safety and preservation throughout the food supply chain.

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Authors' contributions
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REVIEW ARTICLE

Bacterial Proteins and Peptides as Potential Anticancer Agents: A Novel Search for Protein-based Therapeutics

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Abstract: Tumor diseases remain among the world's primary causes of death despite substantial advances in cancer diagnosis and treatment. The adverse chemotherapy problems and sensitivity towards drugs for some cancer types are among the most promising challenges in modern treatment. Finding new anti-cancer agents and drugs is, therefore, essential. A significant class of biologically active substances and prospective medications against cancer is comprised of bacterial proteins and peptides. Among these bacterial peptides, some of them, such as anti-cancer antibiotics and many toxins like diphtheria are widely being used in the treatment of cancer. In contrast, the remaining bacterial peptides are either in clinical trials or under research *in vitro* studies. This study includes the most recent information on the characteristics and mechanism of action of the bacterial peptides that have anti-cancer activities, some of which are now being employed in cancer therapy while some are still undergoing research.

Keywords: Cancer, anti-cancer drugs, bacterial peptides, anti-cancer antibiotics, anti-cancer enzymes, bacteriocins, bacterial toxins, ribosomal peptides.

1. INTRODUCTION

One of the most fatal illnesses in the world is cancer [1, 2]. Cancer is a disorder in which one or more cells are unable to control their growth, leading to either liquid cancer or a firm clump called a tumor [3, 4]. In 2012, almost 14 million cases of cancer were recorded. Cancer was the cause of 8.8 million fatalities in 2015, and according to the Global Cancer Statistics Report, in 2020, 19.3 million cases were recorded, and roughly 10 million people passed away from the disease [5]. The most frequent causes of mortality were malignancies of the lung, liver, colon, stomach, and breast [6]. The main treatments involve radiotherapy, surgery, and/or chemotherapy [7, 8]. Low-molecular-weight drugs are used in chemotherapy to either kill tumor cells specifically or, at the very least, control their growth. According to how they work, anti-cancer drugs can be categorized as hormones, monoclonal

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antibodies, molecular targeting agents, or other biological agents [9, 10]. Chemotherapy employs different classes of drugs and natural products, including small molecule agents that act upon a single or a small group of crucial stages in the progression of cancers and dramatically slow down their growth. Such medications have the benefit of frequently being taken orally. As a result of research on the discovery of molecularly targeted cancer therapies over the past few decades, several small molecule medications for the treatment of cancer have successfully entered the clinic. The majority of these drugs work by inhibiting important cancer targets like serine/threonine/tyrosine kinases, matrix metalloproteinases (MMPs), heat shock proteins (HSPs), proteosomes, and other proteins involved in signal transduction pathways [11, 12]. Another class of medications includes monoclonal antibodies as well as human and/or mammalian (but humanized) proteins [13, 14]. The cytotoxic agents act upon both healthy cells and tumor cells and induce multiple side effects, such as gastrointestinal tract lesions, bone marrow suspension, hair loss, nausea, and clinical development resistance [15, 16]. The therapeutic proteins and peptides from high molecular to medium molecular weight can be used against a broad spectrum of targets with a low restrictive mechanism of action. However, it causes various concerns about severe toxicity, the rapid development of resistance, and side effects [17, 18]. Recently, bacteria and their products have been studied as potential cancer therapeutics [19]. Numerous studies have conclusively shown that bacterial proteins and peptides have anticancer properties. As a promising option in cancer therapies, we summarized anti-cancer bacterial peptides and their mechanisms in the current review.

To achieve the objective of this study, text mining or literature search was limited to published articles listed in Pubmed/ Medline, Pubmed Central, and Google Scholar. We employed both free-text and regulated vocabulary, such as Mesh terms (bacterial proteins or peptides and cancer, bacterial proteins and anticancer, anticancer activity and bacterial peptides or proteins) for bibliographic database searches. This evaluated 1206 articles after duplicate removal. Out of these, 587 were disqualified based on the screening process criteria, as well as the reading of the title and abstract. Furthermore, we evaluated the suitability of 619 papers that had passed preliminary screening and were, therefore, eligible for full-text assessment. Based on our predetermined inclusion and exclusion criteria, 392 articles were excluded, and a total of 227 efficient and related full-text articles were included for the current review, adhering to the guidance of the Preferred Items for Systematic Reviews and Meta-Analyses (PRISMA), as shown in Fig. (**1**). Although the accuracy and completeness of each individual study were checked manually, the risk of bias and certainty of evidence in publications or sources was not examined using any bias or quality check tool.

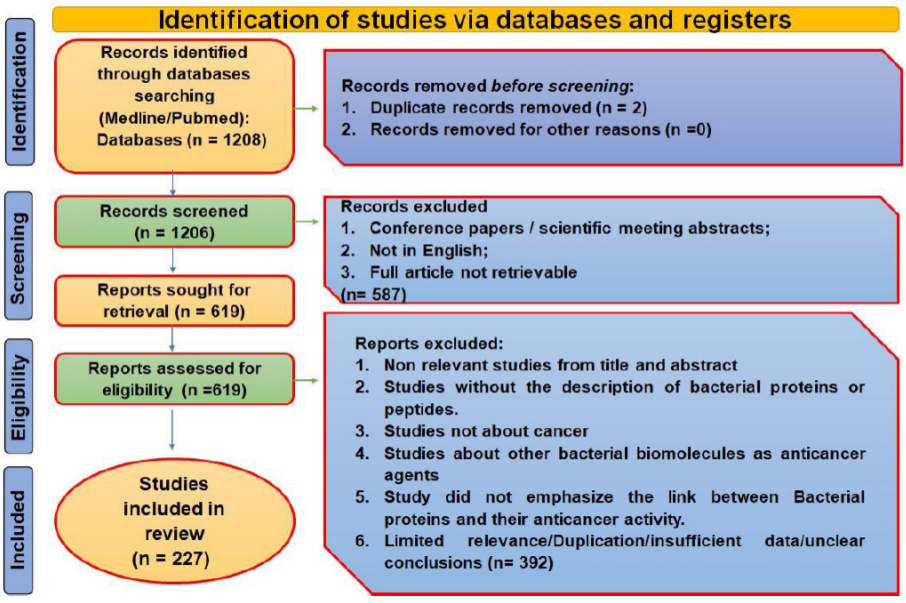

Fig. (1). The PRISMA diagram demonstrates the summary of selecting the eligible literature for the study. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

2. PEPTIDE-BASED ANTI-CANCER THERAPY

The body's natural defensive mechanism depends heavily on antimicrobial peptides (AMPs), which are synthesized by a lot of species, like insects, plants, microorganisms, and mammals. In the dehydration-condensation reaction, combinations of amino acids are joined by peptide bonds to produce compounds known as peptides, which can be obtained from the body's direct synthesis or artificial synthesis [20, 21]. Solution phase synthesis (SPS) and solid phase peptide synthesis (SPPS) are the two major chemical techniques that can be used to synthesize peptides artificially. Although peptides are naturally synthesized in the opposite direction in cells, SPPS is based on the coupling of single amino acids in solution and produces peptides from the carbonyl group side (C-terminus) to the amino group side (N-terminus) of the amino acid chain [20]. Different diseases have benefited from peptide-based therapy. Peptides provide several benefits, including simple availability, straightforward purification, and practical storage. Experimental models using peptide-based therapeutics in both *in vivo* and *in vitro* were analyzed, and some have shown promising results [22, 23].

2.1. Mechanisms of Anti-cancer Peptides

2.1.1. Triggering Tumor Necrosis

Necrosis is the term used to describe the death of living tissue as a result of disease or a disruption in the blood supply. Chromatin flocculation, swelling, and mitochondrial matrix deterioration, cellular membrane blebbing, the contents of cytoplasm being poured into the outer cell spaces are some of the important characteristics of necrosis [24, 25]. Lytic peptides that enable necrosis through membrane disruption are an alluring new class of anti-cancer treatments. Since, these peptides exhibit stronger cancer cell selectivity than conventional chemotherapeutic medications and also do not cause multidrug resistance [26, 27].

2.1.2. Hindering Functional Proteins

A novel treatment strategy to get rid of tumor cells will be to use small peptides to interfere with the unique activities of the many functional proteins that are involved in carcinogenesis and progression. A novel mechanism against motility and metastasis techniques in the stream of oncology may be the binding peptide LS-7, which binds to mouse CD133 and greatly restricts the movement of breast and colon onco--cells in the form of doses depending on each other [28, 29].

2.1.3. Preventing Tumor Angiogenesis

Endothelial cell resettling and multiplication are significant steps in the multi-step process of angiogenesis, which produces vessels of blood from vasculature that are already present. The maturation, attacking, and metastasis of rigid tumors are significantly influenced by angiogenesis, which may supply oxygen and important nutrients and also help in removing waste, such as metabolic waste. Bacterial peptides can inhibit the reactions occurring between receptors and growth factors of angiogenesis, which is how they primarily exert their anti-angiogenic and anti-cancer activities [30, 31].

2.1.4. Apoptosis Induction in Tumors

Multicellular organisms have evolved an innate cell-suicide program called apoptosis to limit cell proliferation as a result of damage of DNA at the stage of development or after cell stress. There is mounting evidence that apoptosis may be crucial in the elimination of onco-cells without causing harm to living cells or living tissues around them. Effective options for curing cancer include targeting apoptotic cycles in both malignant and premalignant cells. Apoptosis is employed as an anticancer technique to eliminate harmful cells and stop the formation of tumors. It prevents cancer by removing cells with potentially dangerous mutations. As novel anti-cancer treatments are developed, peptides enabling apoptosis in tumor cells are becoming increasingly significant molecules [31, 32].

3. BACTERIAL PEPTIDE-BASED ANTI--CANCER THERAPY

3.1. History of Bacterial Peptide-based Therapy

The anti-cancer potential of some bacterial species is evident from various studies, even though bacterial infections with immunogenic nature are thought to be tumor promoters or carcinogenic. Invasion and colonization of solid tumors by various bacterial species have lately demonstrated unexpected potential, leading to tumor suppression. They have additionally been utilized independently or in conjunction with traditional treatment techniques. Prospective bacterial anti-cancer drugs include bacteriocins, peptides, toxins, enzymes, and spores, which are all produced by different bacteria [33, 34]. Since the nineteenth and twentieth centuries, attempts have been made to treat cancer with bacteria and their products. *Streptococcus pyogenes* and *Serratia marcescens* bacterial culture supernatants were used by William Coley [35, 36] to treat patients with unresectable malignancies. About 1200 patients with cancer received treatment with this substance

Table 1. Bacterial peptides as anti-cancer agents.

S. No	Non-ribosomal Peptide	Bacterial species Isolated From	Cancer Effective Against	References
1.	Entap	*Enterococcus sp.*	Colorectal, uterine cervix and breast cancer	[202]
2.	Bacillistatins 1 and 2	*Bacillus silvestris*	Breast and colorectal cancer	[54]
3.	Ariakemicins	*Rapidithrixthailandica*	Lung cancer	[55]
4.	Heptapeptide	*Paenibacillus profundus*	Prostate, lung, and breast cancer	[203]
5.	Lucentamycins	*Nocardiopsis lucentensis*	Colon cancer	[63]
6.	Ieodoglucomides A and B	*Bacillus licheniformis*	Lung and stomach cancer	[204]
7.	Arenamides A and B	*Salinispora arenicola*	Colon cancer	[205]
8.	Halolitoralins A, B and C	*Halobacilluslitoralis*	Gastric cancer	[206]
9.	Padanamides A and B	*Streptomyces sp.*	T cell leukemia	[60]
10.	Ohmyungsamycin A and B	*Streptomyces sp.*	Lung cancer	[207]
11.	Urukthapelstatin A	*Mechercharimyces*	Breast, colon and ovarian cancer	[208]
12.	Piperazimycins	*Streptomyces sp.*	Prostate and breast cancer	[209]
13.	Pep27anal2	*Streptococcus pneumoniae*	Stomach cancer	[210]
14.	Lajollamycin	*Streptomyces nodosus*	Skin cancer	[211]
15.	Mechercharmycin A and B	*Thermoactinomyces*	Lung cancer	[212]
16.	p28	*Pseudomonas aeruginosa*	Breast and skin cancer	[107]
17.	MixirinsA, B and C	*Bacillus sp.*	Colon cancer	[213]
18.	Proximicins A, B and C	*Verrucosispora* strain MG-37	Liver, breast and gastric cancer	[214]
19.	Iturinic Lipopeptides	*Bacillus mojavensis*	Acute myeloid leukaemia	[215]
20.	Azurin	*Pseudomonas aeruginosa*	Breast and skin cancer	[216]

known as Coley's poisons; it frequently resulted in tumor regression and, in 30 individuals, allegedly, a full recovery. Part of the reaction's mechanism has now been identified. Microbiological infections can stimulate the synthesis of cytotoxic substances, particularly tumor necrosis factor (TNF), as well as macrophages and lymphocytes. In an animal model, the anti-cancer effects of TNF were demonstrated by the tumor's full shrinkage and growth suppression [34, 37]. Currently, antiproliferative medicines derived from bacterial proteins and peptides are crucial as these are used in curing cancer.

3.2. Bacterial Peptides as Anti-cancer Agents

Bacterial peptides are protein fragments that bacteria may emit into their surrounding environment that may have anti-cancer effects. Diverse bacterial peptide types are now being researched and identified for their antibacterial and anti-cancer activities [38]. Arenamides, Halitoralins, Idoglobomides A and B, Lucentamycins, Mixirins, Urukthapelstatin, Entap, Pep27anal2, and *Helicobacter pylori* ribosomal protein are some of the most well-known and important bacterial peptides with anti-cancer properties [39, 40]. Numerous studies suggest that bacterial peptides inhibit the growth of cancer cells or induce apoptosis, as well as inhibit angiogenesis, vascular endothelial growth factor receptor 2 (VEGFR2) tyrosine kinase, focal adhesion kinase (FAK), AKT, basic fibroblast growth factor (bFGF) (FGFR-1), and PI3K signaling pathways, and arrest the tumor cell cycle [41, 42]. Table **1** presents the bacterial peptides used as anti-cancer agents along with which cancers they are effective against. Table **1** summarizes various bacterial peptides and their anti-cancer potentials.

3.2.1. Entap

Entap, or enterococcal antiproliferative peptide, is a newly identified anti-cancer peptide that is produced by clinical strains of the bacterium *Enterococcus* genus [43, 44]. Entap's potent antiproliferative effects on human neoplastic cells, such as uterine cervix (HeLa), mammary gland (MDA-MB-231), prostate (22Rv1), and colorectal (AGS) adenocarcinoma cells, have been demonstrated in *in vitro* investigations (HT-29). The antiproliferative effect of entap on cancer cells is demonstrated by the inhibition of their G1 cell cycle and the promotion of autophagic death. Many vacuoles and structures corresponded to autophagosomes and autolysosomes in the cytoplasm of cancer cells exposed to Entap, which led to the discovery of features of degradation and autophagic death. Entap exhibits thermal stability and has a high concentration of hydrophobic amino acids, which gives it a distinctive character [41].

3.2.2. Bacillistatins 1 and 2

Two novel cyclodepsipeptides, Bacillistatins 1 and 2, are produced by the bacteria *Bacillus silvestris* that was identified from a crab from the Pacific Ocean with strong anti-cancer activity against breast and colorectal cancer [45, 46].

3.2.3. Ariakemicins

Two hybrid polyketide-nonribosomal peptides that are linear in structure were produced by the cultivation of the marine gliding bacteria Rapidithrix (ariakemicins A and B). The mentioned proteins displayed modest cytotoxicity towards the lung tumor cell line (A549) of human and kidney cells of young hamsters, as well as antibacterial properties [47, 48].

3.2.4. Heptapeptide

A linear glyceryl acid formed into heptapeptide that is Glyceryl-D-leucyl-D-alanyl-D-leucyl-D-leucyl-D-leucyl-L-valyl-D-leucyl-D-alanine was synthesized by the culture of the marine deep sediment strain SI 79, which is now known as *Paenibacillus profundus.* The peptide exhibits cytotoxic and colony growth inhibitory activity against the melanoma cell line (SK-MEL-28) [49, 50].

3.2.5. Lucentamycins

The 3-methyl-4-ethylideneproline-containing peptides *Nocardiopsis lucentensis* CNR-712, also known as lucentamycins A-D, were separated from the actinomycete strain Nocardiopsis lucentensis broth taken from the sea. Good cytotoxicity was found *in vitro* against human colon carcinoma cells (HCT-116) [51, 52].

3.2.6. Ieodoglucomides A and B

Ieodo Reef's marine sand contains *Bacillus licheniformis*, which is used to make the glycolipopeptides known as ieodoglucomides A and B. They demonstrated cytotoxicity against stomach and lung cancer cells [53-55].

3.2.7. Arenamides A and B

Arenamides A and B, two novel cyclohexadepsipeptides, were separated from the broth that was fermented and has *Salinisporaarenicola*, a marine organism. According to the authors, arenamides A and B prevented TNF from causing activation. Additionally, it was found to decrease the formation of nitric oxide and prostaglandin E2, as well as have a mild effect on cell toxicity in human colon cancer (HCT-116) [56, 57].

3.2.8. Halolitoralins A, B and C

Halobacilluslitoralis YS3106 was discovered in the sea sediments, and it produced two cyclic tetrapeptides (halolitoralin C and halolitoralin B) and a cyclic hexapeptide (halolitoralin A). The cyclopeptides that are presented have sporadic effects on human gastric cancer cells (BGC) [57-59].

3.2.9. Padanamides A and B

Padanamides A and B were generated by *Streptomyces* species that were isolated from marine silt. They were found to suppress the synthesis of methionine and cysteine and are harmful to Jurkat cells. Padanamide A is thought to impede the synthesis of methionine and cysteine according to chemical genomic research into the mechanisms of action of various compounds [58, 60].

3.2.10. Ohmyungsamycin A and B

A volcanic island-isolated strain of *Streptomyces sp*. developed novel cyclic peptides Ohmyungsamycin A and Ohmyungsamycin B. By analyzing the IR, UV, and NMR spectroscopic and MS data of these cyclic peptides, it was possible to reveal the presences of uncommon amino acid units, such as N, N-dimethylvaline, N-hydroxyphenylalanine, and N-methyl-4-methoxytrytophan. Both showed inhibitory effects on a variety of cancer cells, with respective IC50 values within a range of 359 to 816 nM and 12.4 to 16.8μM. Intriguingly, the molecule was more effective in this regard. In contrast to normal cells, cancer cells are more specifically targeted by the compound's anti-proliferative activity. This could result from genetic predisposition or the molecular differences between cancer cells and healthy cells [58, 61].

3.2.11. Urukthapelstatin A

The cultivated mycelia of the *Mechercharimyces asporophorigenens* YM11-542 bacteria, which was found in the sediments of a marine lake, contained the cyclic thiopeptide-urukthapelstatin A. Urukthapelstatin A was particularly effective against ovarian cancer, breast cancer, and colon cancer and demonstrated inhibition of growth in human lung carcinoma cells [62, 63].

3.2.12. Piperazimycins A, B, and C

The fermentation broth of *Streptomyces sp*., which was derived from maritime sediments close to the island of Guam, included three cyclic hexadepsipeptides, piperazimycins A-C. These molecules contain uncommon amino acids, including 2-amino-8-methyl-4,

6-nonadienoic acid and 2-amino-8-methyl-4,6-decadienoic acid, as well as hydroxyacetic acid, 2-methylserine, 2-hydroxypiperazic acid, and 2-chloropiperazic acid. All examined peptides showed cytotoxicity toward various cancer cells [60, 64, 65].

3.2.13. Pep27anal2

Pep27, the peptide for signaling produced by *Streptococcus pneumoniae*, is called Pep27anal2. It also possesses antibacterial qualities and starts the S. pneumoniae death programme mode of antibacterial action of a signal peptide, Pep27, from Streptococcus pneumoniae [66, 67]. Pep27anal2, an obtained analog, was discovered to be a more hydrophobic compound than the parent peptide [68-70]. Considering a similar instance, it was shown that Pep27anal2 permeates the membrane in the cells and causes apoptosis that is not dependent on caspase or cytochrome c. According to the authors, the hydrophobicity of peptides has a significant impact on membrane permeabilization and anti-cancer action [69].

3.2.14. Lajollamycin

Lajollamycin was discovered in the actinomycete *Streptomyces nodosus* NPS007994 found in the sea silt of Scripps Canyon in La Jolla, California, USA. Lajollamycin, a nitro-tetraene spiro-b-lactone-g-lactam peptide, shows antibacterial action and, *in vitro*, suppresses the growth of B16-F10 melanoma cells [70, 71].

3.2.15. Mechercharmycins A and B

A cyclic peptide called Mechercharmycin A and its linear congener Mechercharmycin B were produced by a *Thermoactinomyces specie*s called YM3-251, which was isolated from mud. Mechercharmycin A showed moderately potent anti-cancer activity against Jurkat cells and A549 cells responsible for lung cancer in humans but not mechercharmycin B [45].

3.2.16. p28

One peptide produced from azurin, p28 (Leu50-Asp77), exhibits anti-cancer action in addition to full-length azurin [72]. A tumor-homing peptide that selectively enters tumor cells has been identified as the cell-penetrating peptide p28, Azurin-p28 [73, 74]. The 28 amino acids that makeup p28 are found in the protein azurin (amino acids 50-77) and have an impact on the post-translational rise in p53 and p21 gene expressions, which results in G2-M phase cell arrest [75]. Given that p28 preferentially accesses adult tumor cells as opposed to mature normal cells, one explanation is that the surface of cancer cells has more caveolin (-like) receptors than that of normal cells [76]. Therefore, through the p53 signaling pathway, p28 primarily inhibits cell growth or induces apoptosis. Through transcriptional control of subsequent gene expression, the p53 protein, a transcription factor, mediates DNA damage repair, apoptosis, and cell cycle advancement [77, 78]. It has been shown that p28-stabilized p53 reaches the nucleus and stimulates the production of cell cycle inhibitors like p21 and p27, as well as proapoptotic genes like Bax and Bcl-2. The p53/p21/CDK2 pathway promoted the enhanced antitumor activity of the aforementioned anti-cancer drugs in conjunction with p28 [79, 80].

3.2.16.1. Mechanism of Action

The anti-cancer effects of p28 are also impacted by the presence of p53 in cancer cells. It has been demonstrated that p28 and p53-DBD may communicate. A hub domain called p53-DBD connects to an E3 ubiquitin ligase and COP1, which negatively regulates p53 and is overexpressed in many cancers [81, 82]. The pull-down tests of GST revealed that p28 inhibits COP1's ability to attach to p53-DBD, where it depends on concentration, indicating that p28 and COP1 are competitors for this binding site. The simulated models show that p28 competes with COP1 for binding to p53-DBD by attaching to a pocket at Trp146. As p28 prevents COP1 from binding to p53-DBD, one potential mechanism by which p28 stabilizes p53 is through the COP1-mediated ubiquitination pathway. It is possible to use p28 rational designs to produce large levels of affinity for different p53 mutants. The cytokine vascular endothelial growth factor (VEGF), which encourages angiogenesis, is frequently overexpressed in solid tumors and blood malignancies. An important factor controlling angiogenesis in tumors is the interaction between VEGFA and its receptor VEGFR-2 [83]. In numerous xenograft models, it was discovered that p28 suppresses VEGF-induced migration, capillary tube production, and neoangiogenesis. FAK and Akt's downstream phosphorylation is reduced by p28, which leads to an aberrant distribution of proteins involved in cell migration. To further understand the angiogenic effect that is anti-cancer on endothelial cells with p28, additional research on the relationships between p28 and VEGFR-2 will be helpful [79, 84].

3.2.17. Mixirins A, B, and C

From a marine bacterium termed *Bacillus sp*. that was found in mud present in seas in the Arctic pole, three different cyclic acylpeptides, known as mixirins A-C, were identified. All the mixirins helped block the growth of the human colon tumor cell line (HCT-116) [85-88].

3.2.18. Proximicins A, B and C

From the marine strain MG-37 of the uncommon species Verrucosispora, three new aminofuran antibiotics (proximicins) were discovered. The compounds present showed inhibition potential in growth against cell lines of gastric adenocarcinoma, hepatocellular carcinoma, and breast carcinoma. After 24 hours of incubation, Proximicin C caused cell arrest in the G0/G1 phase, according to an examination of the cell cycle in AGS cells. The number of cells in the sub-G1 phase, or apoptotic cells, increased after 40 hours. Additionally, it was discovered that proximicin C causes the cyclin kinase inhibitor p21 as well as p53 to upregulate in AGS cells [55, 87, 89].

3.2.19. Iturinic lipopeptides

Bacillus mojavensis B0621A, which was extracted from the South China Sea pearl oyster Pinctada martensii, contained three iturinic lipopeptides. The three lipopeptides were weak in cytotoxic activities against human leukemia (HL-60) cell lines [90, 91].

3.2.20. Azurin

Pseudomonas aeruginosa produces a protein called azurin, a single-domain protein with a stiff-barrel structure that contains copper. The drug Azurin has a hydrophobic patch. A resolution of 1.85 A was used to identify the 3D structure of apo-azurin from *Pseudomonas aeruginosa*. Two distinct molecular structures of apo-azurin are arranged in the tetramer of the asymmetric unit as hetero-dimers to generate the crystal structure with four chains, A, B, C, and D, respectively, as shown in Fig. (**1**). Azurin is a redox protein that belongs to the cupredoxin family. The copper of the azurin can be removed, resulting in apo-azurin [92, 93]. The apo-azurin exhibits considerable cytotoxicity while having very modest redox activity (0.02 and 0.01% of the holoenzyme wt azurin). Azurin appears to be dependent on the stability of the p53 protein, which prevents the growth of cancer, to be able to kill tumor cells. Azurin increases the amounts of p53 and Bax inside the nucleus, which causes the release of mitochondrial cytochrome c into the cytosol. This mechanism starts the apoptotic process by activating the caspase cascade, which includes caspase-7 and caspase-9. The anti-cancer activity of Azurin has been attributed to several different mechanisms, including (i) inducing cancer cell apoptosis or growth inhibition by forming complexes with tumor protein p53; (ii) inhibiting cancer cell growth by interfering with the receptor tyrosine kinase EphB2-mediated signaling process; (iii) inhibiting tumor growth by preventing angiogenesis by reducing VEGFR-2 in the breast cancer cell line (MCF-7). In a study, a peptide demonstrated a potent cytotoxic impact that caused a more than 50% increase in apoptosis; however, it was not effective against other breast cancer cells (MDA-MB-157, MDD2, MDA-MB-231). In additional tests, it demonstrated anti-cancer effectiveness against melanoma cells and YD-9 oral squamous carcinoma cells [94-96]. A crystalline structure for azurin has been illustrated in Fig. (**2**).

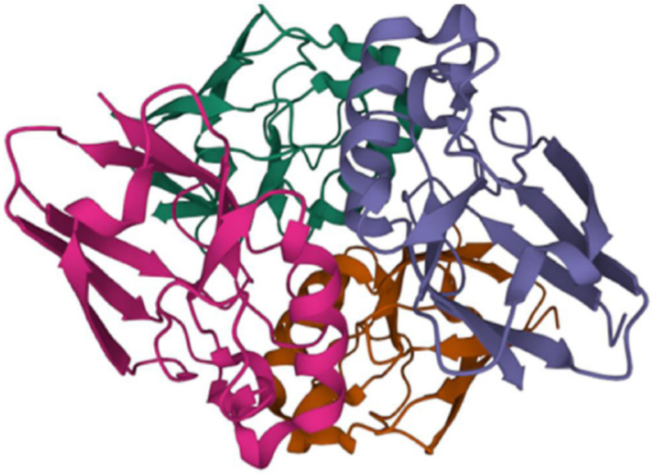

Fig. (2). Crystalline Structure of Azurin from *Pseudomonas aeruginosa* (PDB ID 1E65). (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

3.2.20.1. Mechanism of Action

Redox signaling is mediated by reactive oxygen species (ROS) for several biological processes [97]. Cell death is typically caused by cells with high amounts of ROS. As a result, options for cancer treatment may be provided by modulating ROS levels [98-100]. Azurin, an oxidoreductase (redox) protein, demonstrates cytotoxic activity towards macrophages by producing elevated amounts of reactive oxygen species (ROS) and forming complexes with the tumor-suppressor protein p53. Mechanistic investigations of azurin and its mutations imply that it enables redox homeostasis through a mechanism using the p53 gene [101, 102]. Studies have reported that the anti-cancer efficacy of azurin is dependent on the existence of the p53 protein [103]. A significant E3 ubiquitin ligase called MDM2 enables the N-terminal transactivation domain of p53 to bind and control the degradation of that protein (p53-TAD). Azurin/p53-TAD complex has a substantially higher dissociation constant (Kd 7 nM) than MDM2/p53-TAD complex (Kd 34 nM). Molecular docking and Raman spectroscopy were used to investigate the communication between the p53 DNA-binding domain (p53-DBD) and azurin, which showed

that binding was possible to azurin and boost its structural stability. The protein level and activity against cancer of p53 may be related to the structural stability of p53-DBD [102, 104]. Cell shape, cell migration, and membrane stiffness are only a few of the ways through which cell-surface receptors control the structural characteristics of the membrane of the cell. As a result, the leveling of the receptors used for cell surfacing expression influences how effective anti-cancer medications can act [105]. In A549 lung cancer cells, Bernardes discovered that azurin lowered the integrin 1 levels expression, leading to disruption in the distribution of the protein on the cell membrane. Azurin treatment alters the surface structure of onco-cells, making them more susceptible to chemotherapy and anti-cancer medications, like gefitinib and erlotinib, which target the epidermal growth factor receptor (*e.g.*, paclitaxel, doxorubicin) [105]. As Src, FAK, P13K, and Akt phosphorylation levels are typically reduced, the modification of cell membrane characteristics by azurin may potentially be related to the intracellular signaling responses of non-receptor tyrosine kinases [106, 107].

3.3. Enzymes as Anti-cancer Agents and Their Mechanism of Action

Biological polymers that catalyze biochemical reactions are known as enzymes. There are several enzymes found in bacteria that can be used to treat cancer. Tumors grow quickly, which causes some enzymes to express less, which causes auxotrophy for some particular amino acids. Amino acid-depleting enzymes target these auxotrophic malignancies. Since normal cells can produce amino acids using their regular machinery, the reduction in amino acids specifically slows the growth of tumors. Arginine deiminase, L-asparaginase, and Methioninase are some examples of enzymes derived from bacteria that are used in the therapy of specific cancer disorders [108, 109].

3.3.1. Methioninase

Methioninase, also known as methionine gamma-lyase, is a member of the group of enzymes that are dependent on pyridoxal L-phosphate (PLP). It is an enzyme that catalyzes the gamma and alpha elimination of L-methionine by converting it to ammonia, methanethiol, and alpha-ketobutyrate. An important amino acid for humans that contains sulfur is l-methionine. Apart from the synthesis of proteins, it also has a vital role in behaving as a precursor of S-adenosyl methionine (SAM), glutathione, and polyamines. SAM is necessary for the methylation of proteins, RNA, and DNA, whereas glutathione is important for the function of cellular antioxidant systems, and polyamines are required for nucleotide synthesis and cell division. Antioxidant mechanisms, altered epigenetic alterations of tumor cells, and decreased histone methylation may all contribute to tumor cells' methionine dependence [110-112].

3.3.1.1. Mechanism of Action

Compared to normal cells, tumor cells proliferate and multiply at an uncontrollably high rate. For the control of DNA expression in cancer cells and increase in protein synthesis, several malignant human cell lines increase methionine needs. Methionine becomes S-adenosylmethionine and serves as a donor of a methyl group for the methylation of DNA, an epigenetic process linked to cancer [113-115]. A higher risk of prostate cancer was linked to diets high in methionine. With the increased accessibility of S-adenosylmethionine as a donator of methyl groups to deoxyribonucleic acid as a result of increased L-methionine availability, regulatory sections of the DNA, including tumor suppressors, become hypermethylated. The instability of the genome and proto-oncogene activation is caused by hypomethylation of miRNAs. The hypermethylation of the relevant promoter sites suppresses the expression of tumor suppressor miRNAs. The miRNAs control how genes are expressed both within a cell and in nearby cells [116-118].

Malignant cells are deprived of essential growth factors in the presence of L-Methioninase, which causes exhaustion of methionine. Eventually, the tumor cells will be arrested, most commonly in the late S/G2 phase of the cell cycle, and will die. Fig. (**3**) below shows the mechanism of L- Methioninase against cancer cells.

3.3.2. L-asparaginase

Escherichia coli or Erwinia species have the L-asparaginase (ASNase) enzyme. It facilitates L-asparagine hydrolysis into aspartate and ammonia. These are usually precursor molecules when synthesized. The activation of this molecule is done by autoproteolytic release of two subunits, alpha and beta. It is classified as a non-essential amino acid, which is crucial for immune system function as well as the synthesis of proteins and glycoproteins. In this way, asparagine depletion presents a potential strategy for the elimination of asparagine auxotrophic tumor cells. The capacity of bacterial ASNases to lower asparagine blood concentrations results in a selective reduction of the proliferation of vulnerable malignant cells, which is what gives these enzymes their anti-tumor effects [119-121]. The be-

low-mentioned cell lines for brain tumours were treated with ASNase *in vitro* and showed dose-dependent growth inhibition: p53, a paediatric medulloblastoma (DAOY) and PTEN-deficient human glioblastomas (GBM-ES and U87) [122, 123]. Hodgkin's and non-Hodgkin's lymphomas, myeloblastic leukemia, extranodal NK/T cell lymphoma, Acute lymphoblastic leukemia (ALL), myelosarcoma, multiple myeloma, and ovarian carcinomas have all recently been treated with ASNase [124, 125]. The crystalline structure of L-asparaginase and interactions between L-asparaginase and target ligand L-asparagine are illustrated in Fig. (**4**).

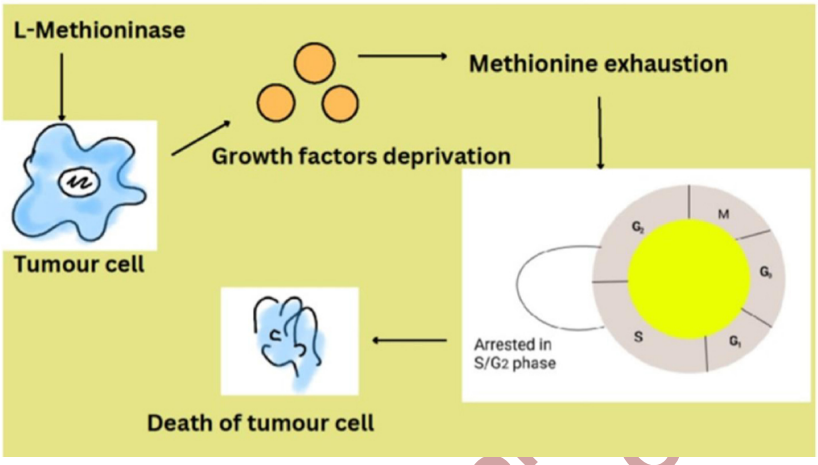

Fig (3). Mechanism of L-Methioninase against Tumour Cells. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

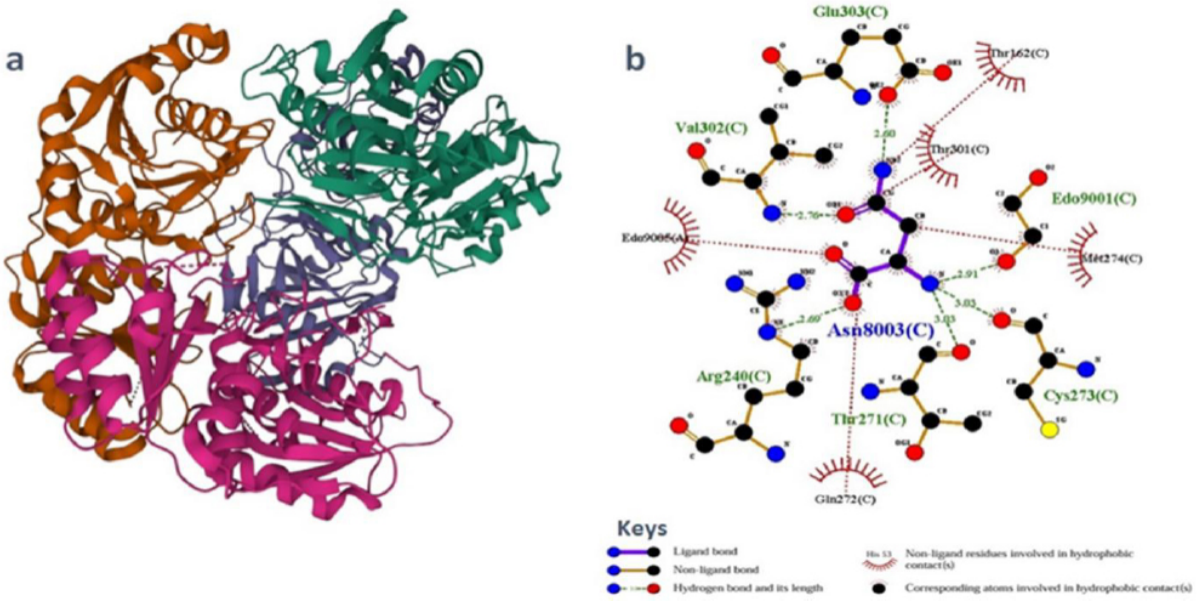

Fig. (4). (**a**) Crystalline structure of L-asparaginase from *Escherichia coli* (PDB ID: 2P2N); (**b**) Interactions between L-asparaginase and target ligand L-asparagine. (**a**)The crystallographic structure reveals that cytoplasmic L-asparaginase forms a tetrameric structure as a dimer of two intimate dimers and is involved in intracellular asparagine utilization; (**b**) Interactions between L-asparaginase and target ligand L-asparagine (Analysis and 2D representation of protein-ligand interactions of the PDB structures were done using LIGPLOT). (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

3.3.2.1. Mechanism of Action

A non-essential amino acid called asparagine helps cells grow and maintains the synthesis of ribonucleic acid, proteins, and deoxyribonucleic acid. While the cells of lymphoblastic leukemia are devoid of the asparagine synthetase enzyme and are, therefore, unable to create asparagine from scratch, healthy and normal cells can receive asparagine through dietary intake or synthesize the amino acid from aspartate through asparagine synthetase activity [126]. Leukemic cells, therefore, depend on asparagine from an exogenous source for cell survival and the synthesis of protein. By converting L-asparagine from *E. coli* to L-aspartic acid and ammonia, which reduces ribonucleic acid, deoxyribonucleic acid, and synthesis of protein, inhibits cell development and ultimately activates apoptotic cell-death processes, L-asparagine from *E. coli* works to deplete plasma levels of asparagine in leukemic cells. However, because normal cells can manufacture their asparagine, they are less impacted by the asparaginase treatment's quick depletion [127]. The linear structure of L-asparaginase is shown in Fig. (**5**).

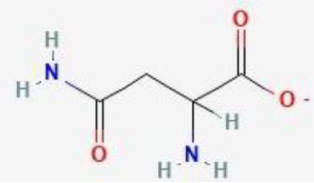

Fig. (5). Linear structure of L-asparaginase from *Escherichia coli.* (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

3.3.3. Arginine Deiminase

Mycoplasma hominis or *M. arginini* secretes an enzyme called arginine deiminase (ADI) that enables an arginine to citrulline conversion *in vivo* and releases ammonia. The native form of arginine deiminase is highly immunogenic. Protein synthesis in cancer cells, apoptosis, and angiogenesis is inhibited by the addition of ADI. As arginine is required for the production of NO, tumor cells treated with ADI have lower levels of nitric oxide (NO) synthetase. A growth factor, namely vascular endothelial growth factor, is a crucial component necessary for the angiogenesis of tumor cells and is biosynthesized in considerable amounts by NO. Due to this, tumor cells are unable to multiply in the absence of NO. Hepatocellular carcinoma with argininosuccinate synthase deficiency or arginine auxotrophic growth may be controlled by arginine deiminase (HCC) [85, 128, 129]. Pegylated ADI is the medication that takes advantage of the high enzymatic deficit in HCC and exhibits considerable disease-stabilizing activity in HCC. The lack of argininosuccinate synthase is directly connected with the effectiveness of ADI-PEG20. It is used in the treatment of hepatocellular carcinoma, prostate cancer, and glioblastoma [130-132]. The crystalline structure of arginine and interactions between arginine and target ligand arginine deaminase is illustrated in Fig. (**6**).

3.3.3.1. Mechanism of Action

Studies conducted *in vitro* have revealed that arginine deprivation causes cancer cells to perish while causing normal cells to undergo the G1 cell cycle halt. The detection of tumors auxotrophic for arginine results from the culture of cancer cells in a medium deficient in arginine. The expression of the apoptosis inhibitor survivin and intestinal hyperproliferation may be prevented by L-arginine, which also greatly increases nitric oxide synthase [7, 132]. Citrulline can be converted into arginine in normal cells by the enzyme argininosuccinate synthetase (ASS), whose expression is closely controlled. Unknown processes, however, cause the expression of ASS to be downregulated in some tumor cells, preventing these cells from converting citrulline to arginine. To develop and function properly, the tumor cells become auxotrophic for arginine. ASS (+) ADI-resistant normal cells are spared when arginine auxotrophic ASS tumour cells are deprived of arginine by the use of ADI. The prevalence of ASS deficiency varies with the kind of tumor, and the degree of ASS expression has been suggested as a biomarker for detecting ADI-sensitive cancers [133].

3.4. Bacterial Bacteriocins as Anti-cancer Agents

According to the definitions, bacteriocins, which are produced by all types of bacteria on a ribosomal basis, are a form of cationic peptide. A few of them also exhibit anti-cancer properties. It has been demonstrated that the physiological actions of bacteriocins are dependent on preventing the growth or eradication of rival microorganisms, whether they are known or unrelated strains of bacteria, in a certain niche that is biologically active [134]. Additionally, bacteria that make these peptides are resistant to their respective bacteriocins. Microcins, colicins, and tailocins are three types of bacteriocins that enable the production of gram-negative bacteria that are distinguished by their molecular weight or size. Bacteriocins can inhibit the growth of tumors through a variety of mechanisms, including (i) non-specific DNase activity, (ii) inducing apoptosis, (iii) cell shrinkage, (iv) forming pores in the plasma membrane, (v) cell cycle changes, (vi) preventing protein synthesis through the breakdown of 16S rRNA or tRNAs, (vii) necrosis, and (viii) DNA fragmentation [135].

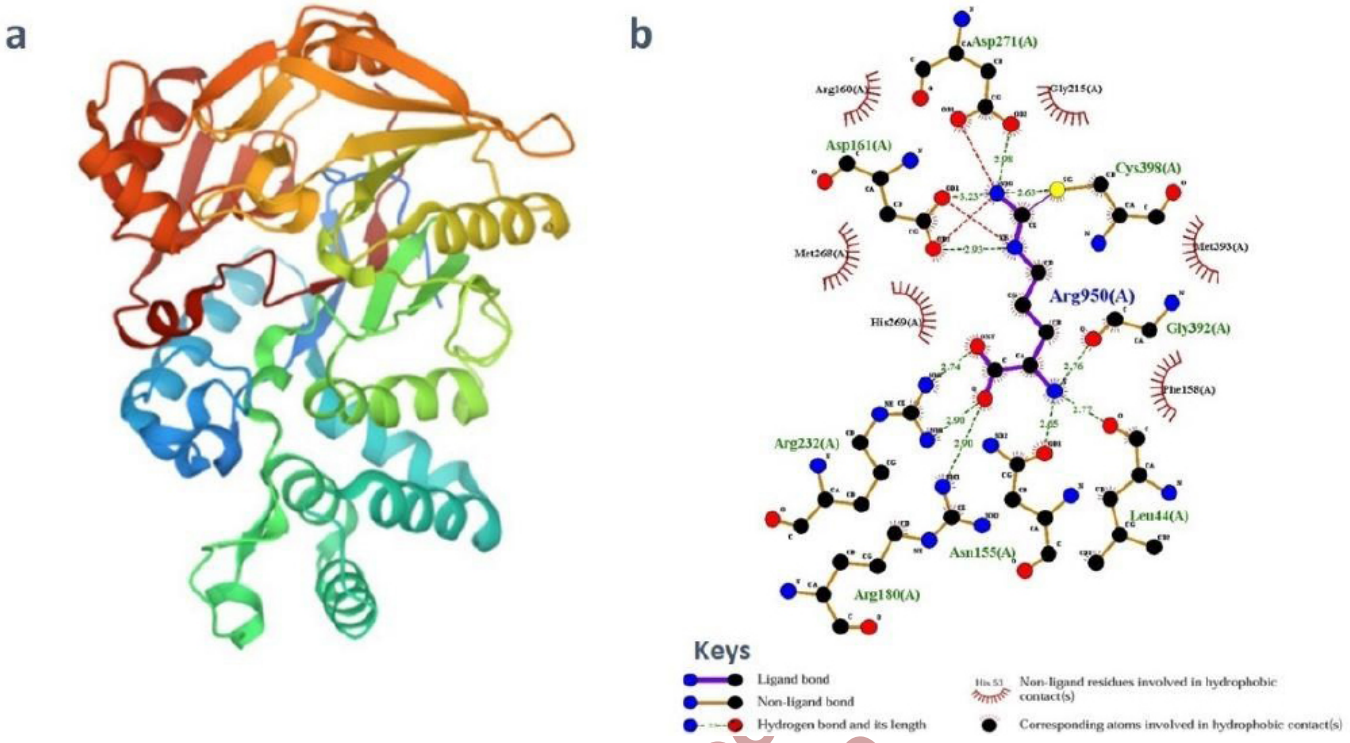

Fig. (6). (**a**) Crystalline Structure of Arginine Deiminase from *Mycoplasma* spp. (PDB ID:4E4J); (**b**) Interaction between Arginine and Arginine Deaminase (PDB ID:1S9R) (Analysis and 2D representation of protein-ligand interactions of the PDB structures were done using LIGPLOT). (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

3.4.1. Classes of Bacteriocins

3.4.1.1. Class I

Lantibiotics are short (5 kDa) peptides with distinctive polycyclic thioether amino acids like methyllanthionine and lanthionine as well as unsaturated amino acids like 2-aminoisobutyric acid and dehydroalanine. Based on the difference in charge, lantibiotics are further divided into two categories. Type A includes lantibiotics, such as lacticin 3147 and nisin, which are positively charged and result in the formation of pores in the membrane of the organism targeted. Type A lantibiotics, like nisin and lacticin 3147, are 2-4 kDa positively charged, screw-shaped, flexible molecules that cause pore development in the cell membrane of the target organism and consequently cause the cytoplasmic membrane of the target species to depolarize. 2-3 kDa peptides known as Type B lantibiotics are either net-charge-free or net-negatively charged. These molecules are globular in shape and obstruct cellular enzymatic processes like the creation of cell walls [136].

3.4.1.2. Class II

A leader peptide is removed, and a conserved N-terminal disulfide bridge is formed to create Class II bacteriocins, which are short (10 kDa), non-lanthionine--containing and heat-stable peptides. They can be inserted into the target cell's membrane due to their amphiphilic helical nature, which causes depolarization and death. Class II bacteriocins are further divided into subclasses a, b, and c, which differ in their structural composition and mechanism of action [137].

3.4.1.3. Class III

Heat-sensitive peptides with high molecular weight (>30 kDa) fall under the category of class III bacteriocins. This class includes some of the members of colicins, Klebicin, and enterolysin [45]. Fig. (**6**) shows various classes of bacteriocins. Different classes of bacteriocins are shown in Fig. (**7**).

3.4.2. Microcin E492

A bacteriocin called microcin E492 (M-E492) is created by *Klebsiella pneumoniae* RYC492. They release powerful antibacterial action against closely

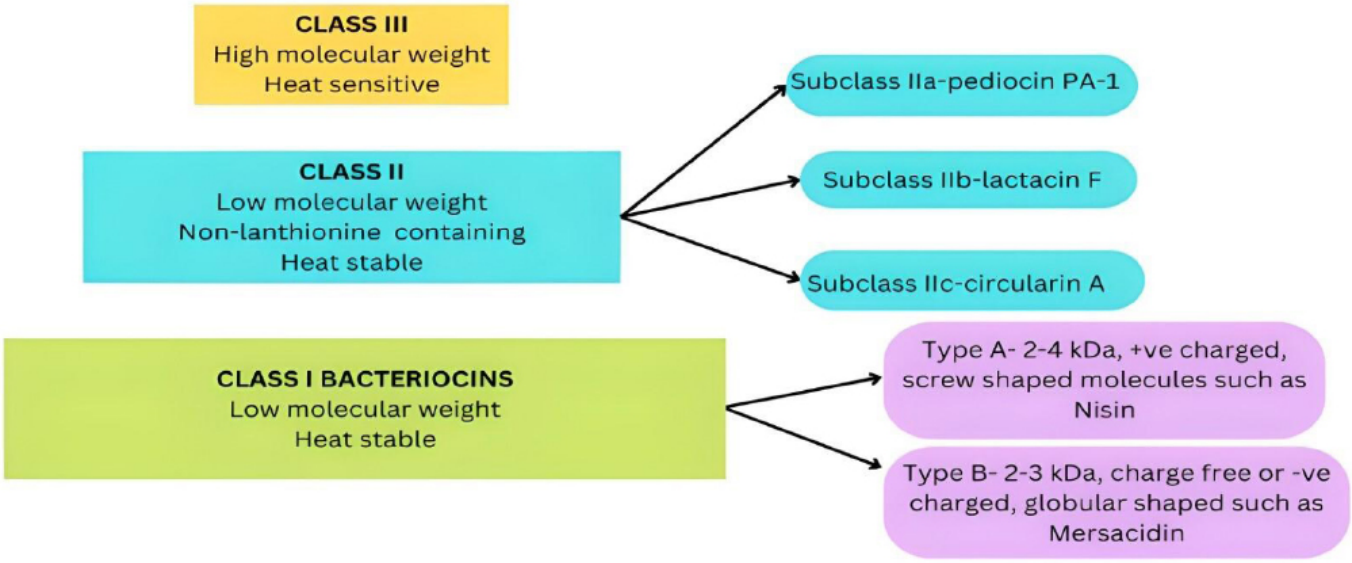

Fig. (7). Different Classes of Bacteriocins. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

related organisms when there is a lack of nutrients [45]. Several malignant human cell lines, including acute T cell leukemia (Jurkat), B-lymphoblastoid cell lines, cervical adenocarcinoma (HeLa), a B cell line derived from Burkitt's lymphoma (Ramos) converted by Epstein-Barr virus infection, were found to be cytotoxic to M-E492 (RJ2.25, a variant of the Raji B-LCL). Previous research demonstrated that membrane potential disturbance and the creation of pores cause microcrin E492 to cause direct cytotoxicity in cancer cells [138]. Cell shrinkage, DNA breakage, extracellular exposure of phosphatidylserine, drop in membrane potential of mitochondria, caspase activation and release of calcium ions from intracellular reserves were among the morphological and biochemical changes caused by M-E492 during apoptosis [139].

3.4.3. Smegmatocin

Mycobacterium smegmatis 14468 produces the bacteriocin smegmatocin. The bacteria in the culture supernatant do not release smegmatocin. Therefore, the cells are ultrasonically treated to liberate the bacteriocin in the culture supernatant, which is then used to purify smegmatocin. Proteolytic enzymes, including chymotrypsin, pepsin, and trypsin, inactivate it [140]. In comparison to a control smegmatocin preparation that had been heat-inactivated, HeLa S3 cells were treated for 96 hours with smegmatocin at concentrations of 64 and 128 AU/ml. This resulted in a nearly 1-log reduction in the number of viable cells. Morphological alterations in the cancer cells included the emergence of vacuoles in their cytoplasm and shrinkage. Smegmatocin is a fairly big protein, and it is unknown how it acts and is taken up by eukaryotic cells; thus, more research is needed to ascertain its mode of action against human cancer cell lines [45].

3.4.4. Bovicin HC5

The lantibioticbovicin HC5 is produced by *Streptococcus bovis*. It is physically and functionally comparable to nisin and is stable to low pH and autoclaving. It possesses broad-spectrum antibacterial activity against several different Gram-positive and Gram-negative bacteria, including closely related strains of *S. bovis* [141]. The principal method of action involves creating pores in the cell membrane, which leads to an ionic imbalance that specifically affects potassium efflux in the target cell. It is used for treating human breast adenocarcinoma and human liver hepatocellular cancer [142].

3.4.5. Plantaricin A

Plantaricin A is a bacteriocin of *Lactobacillus plantarum* C11. Different glycosylation patterns are thought to have anti-cell-type effects, particularly those on malignant cells. It has cell toxicity against the Jurkat, which is human T-cell leukemia. Plantaricin Jurkat cell line underwent apoptosis and necrosis, as evidenced by the disintegration of the cell plasma membrane and nuclei [143].

3.4.6. Nisins

A polycyclic antimicrobial peptide made by *Lactococcus lactis*, nisin, has 34 amino acids. According to recent studies, nisin increases cell apoptosis by activating CHAC1, boosting calcium influxes, and inducing cell cycle arrest. This reduces the carcinogenesis of head and neck squamous cell carcinoma (HNSCC). In HNSCC cells, Nisin ZP, a natural variation of Nisin, significantly increased apoptosis. Indeed, as the concentration of nisin ZP increased, apoptosis gradually increased. In HNSCC cells, apoptosis was induced *via* a calpain-dependent mechanism. Human umbilical vein endothelial cells (HUVEC) were also made to undergo apoptosis, which decreased the density of the microvessels inside the tumor [144]. Nisin's cytotoxic activity was recently tested on colon cancer SW480 cells, where it significantly reduced cell proliferation and increased apoptosis. Additionally, nisin and doxorubicin's synergistic action demonstrated a considerable decrease in tumor volumes when compared to the use of these drugs alone [145].

3.4.7. Laterosporulin 10

Laterosporulin 10 (LS10), a defensin-like peptide that inhibits microbial infections, is isolated from *Brevibacillus sp.* The examination of LS10's amino acid composition revealed that amino acids of hydrophobic nature predominated, and it is capable of eradicating the Mtb H37Rv strain found inside the phagosomes located in the murine macrophages. Even at higher concentrations, macrophage cells were shown to be unaffected [146]. Changes in ATP levels and NAD(P)/-NAD(P)H ratios showed that this was also implicated in membrane disruption. RBCs were unaffected since no hemolysis was seen, even at concentrations higher than their MIC values [147]. Moreover, it has been demonstrated that it has anti-cancer activity against fibrosarcoma (HT1080), cervical cancer (HeLa), lung carcinoma (H1299), breast cancer (MCF-7), and embryonic kidney cancer (HEK293T) [45]. In cancer cell lines, a dose-dependent cytotoxic activity was seen; at lower concentrations, the chemical caused cancerous cells to undergo apoptosis, but at larger levels, it led to necrotic death [146].

3.4.8. Pediocins

Pediocins are bacteriocins that fall under class IIa. *Pediococcus acidilactici* MTCC 5101 produces pediocin CP2. Pediocins are extremely stable peptides that work well in a variety of pH and temperature conditions. However, proteolytic enzymes, including trypsin, pepsin, protease, alpha-chymotrypsin, and papain, might make them vulnerable. The "pediocin box," or conserved motif Y-G-N-G-V/L, and two conserved cysteines that are connected by a disulphide bridge to form a three-stranded antiparallel beta-sheet structure are found in the N-terminal region of pediocins [148, 149]. While the interaction is mediated by the cationic-sheet domain at the N-terminal, the hairpin-like C-terminal area is responsible for the peptide's entry into the hydrophobic part of the target cell membrane. It is also used to treat hepatocarcinoma (HepG2), cervical adenocarcinoma (HeLa), cervical adenocarcinoma (HeLa), and adenocarcinoma (MCF-7) [150].

3.5. Bacterial Toxins as Anti-cancer Agents

For the treatment of advanced solid tumors, bacterial toxins with antitumor activity have been developed as an alternative to chemotherapy. Tumor-specific antigens are frequently abundant on the cell surface of cancer cells, where they bind to bacterial toxins and cause them to become active. The toxins that bacteria make are the kind of chemicals that can target host cells and kill those cells and tissues by acting in a very powerful way. They play important roles in determining how the infection will turn out by altering cellular functions, causing cell death, and changing the proliferation of cells and differentiation. Some toxins of bacteria have a lot of promise for treating cancer. Table **2** summarizes bacterial toxins and their applications in cancer therapy.

Table 2. Different bacterial toxins used in cancer therapy.

S.No	Bacterial Toxin	Bacteria Isolated From	Type of Cancer Effective Against	References
1.	*Clostridium perfringens* enterotoxin	*Clostridium perfringens*	Colon cancer	[217]
2.	Listeriolysin O	*Listeria monocytogenes*	Breast cancer	[218]
3.	Botulinum Neurotoxin Type A	*Clostridium botulinum*	Prostate and breast cancer	[219]
4.	Exotoxin A and T	*Pseudomonas aeruginosa*	Pancreatic cancer	[220]
5.	Verotoxin 1	*E.coli*	Lung cancer	[221]
6.	Diphtheria Toxin	*Corynebacterium diphtheriae*	Adrenocortical cancer	[222]

3.5.1. Clostridium Perfringens Enterotoxin (CPE)

Numerous studies have demonstrated the anti--cancer benefits of *Clostridium perfringens* enterotoxin, a pore-forming bacterial toxin that has been successfully employed in cancer therapy, particularly in the treatment of colorectal cancer. Claudin receptors, which are a part of the tight junction, bind to native CPE. Before this oligomer is inserted into membranes to produce an active pore, the attached toxin first forms a hexametric prepore on the membrane surface. For cells displaying high levels of claudin-3 or -4, which includes many cancer cells, the toxin is particularly deadly (P. C. Sharma *et al.*, 2022). According to preliminary research, native CPE may be effective in treating several malignancies when there is an overexpression of claudin CPE receptors. Cells devoid of CPE receptor expression are completely unaffected by this enterotoxin, whereas CPE can cause the lysis of epithelial cells by binding to claudin-3 and claudin-4, resulting in the onset of major permeability alterations, osmotic cell ballooning, and cytolysis [151, 152].

3.5.2. Listeriolysin O

Listeria monocytogenes strain, a pathogen that grows in the cytoplasm of cells, produces listeriolysin O (LLO). This molecule is essential for the bacterium's phagosomal egress into the cytoplasm. The crystal structure of LLO helps in polymerization and oligomerization. Mutations in a cancer cell are determined by calcium uptake and haemolytic activity. Breast cancer cell lines were effectively eliminated by the conjugated immunotoxin B3-LLO in SKBR-3 and MCF7 [153]. Fig. (**8**) illustrates the crystalline structure of listeriolysin.

3.5.3. Botulinum Neurotoxin Type A

The toxin of bacteria with anti-cancer potential, botulinum neurotoxin type A (BoNT-A), is produced by *Clostridium botulinum*. After entering tumor cells, BoNT-A binds to the SV2 receptor and inhibits cell growth and proliferation while causing apoptosis, which is dependent on caspase-3 and caspase-7, to treat various cancers [154, 155]. Due to its apoptotic activity, botulinum neurotoxin type A is used to treat benign prostatic hyperplasia (BPH). The proliferation and expansion of prostate carcinoma cell lines (PC-3 and LNCaP) are likewise decreased by the toxin. Additionally, in cancers, like breast cancer, botulinum toxin A triggers caspase-3 and -7 dependent apoptotic pathways (T47D) [156, 157].

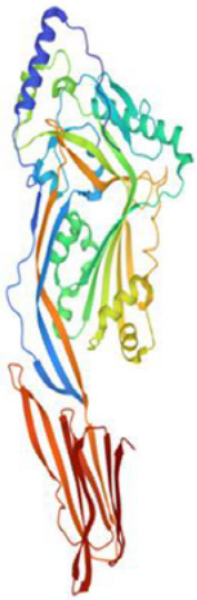

Fig. (8). The crystalline structure of listeriolysin O has one chain (chain A) of sequence length 488 amino acids from *Listeria monocytogenes* (PDB ID: 4CDB). (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

3.5.4. Exotoxin A and T

Exotoxin A (PE) and Exotoxin T (ExoT) are most commonly produced by *Pseudomonas aeruginosa* and exhibit strong anti-cancer potential by causing apoptosis in cancer cell types. With various ligands, exotoxin is typically used as an immunotoxin. Interleukin 4 and Human epidermal growth factor (EGF) cloned *Pseudomonas* exotoxin exhibited effectiveness against pancreatic cancer (PaCa-2) and specifically inhibited metastasis [158]. By controlling the C10 regulator kinases, cell cycle progression, skeletal actin dynamics, activation of protein kinase, cytokinesis, and ExoT can target several crucial cellular proteins that are effective in various processes, including angiogenesis, survival, proliferation, and metastasis as well as in cancer-causing cells. Angiogenesis is crucial for the progression of cancer [159].

3.5.5. Pathotypes of E. coli

Verotoxin 1 (VT1 or Shiga toxin-1 (Stx-1)) is a toxin that is produced by some pathogenic types of *E. coli*, notably VT-producing E. coli (VTEC) and enterohemorrhagic *E. coli* (EHEC). Through a variety of mechanisms, including cell cycle arrest, fragmentation of DNA, and altered expression of cell cycle proteins, VT-1 demonstrates anti-cancer efficacy (Lingwood, 2020) [160].

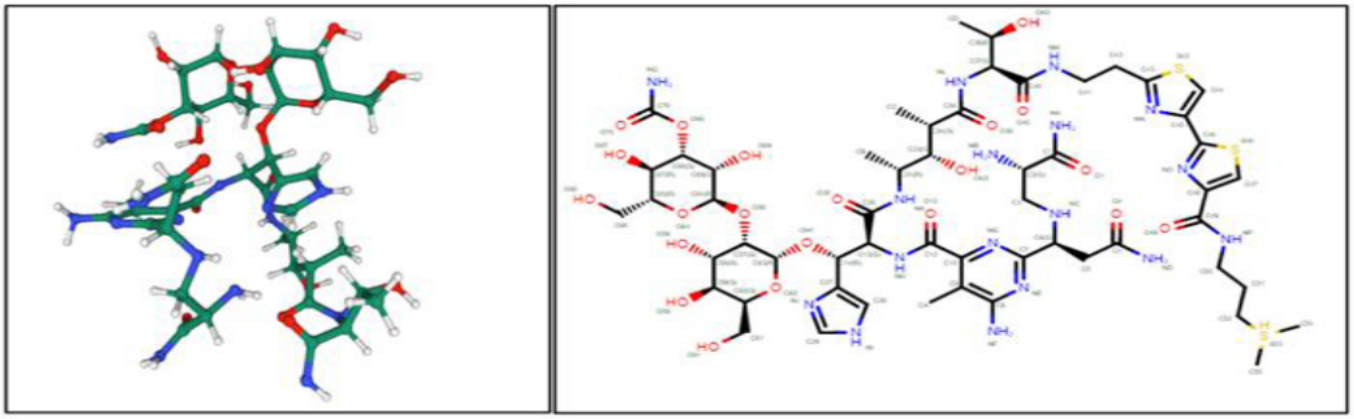

Fig. (9). The Linear (2D) Structure of Bleomycin from *Streptomyces verticillus* (PDB ID: 1UGT). (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

3.5.6. Diphtheria Toxin

Corynebacterium diphtheriae produces an exotoxin known as diphtheria toxin (DT). DT has anti-cancer properties, but it has negative effects. Hence, it is used in antitumor therapy in conjunction with other drugs. The harmless variant of diphtheria toxin called the cross-reacting material 197 (CRM197) binds to Heparin-binding epidermal growth factor-like growth factor. Inhibiting angiogenesis and promoting cell death in human adrenocortical cancer was demonstrated by CRM197 (H295R) [161].

3.6. Antibiotics as Anti-cancer Agents and Their Mechanism of Action

Antibiotics are referred to as chemical substances that are mostly produced by microbes and harmful to other members of this class. Some antibiotics are found to have anti-cancer activity, and lately, they have primarily been employed as antitumor medications [162]. Research has shown that antibiotics can stimulate cancer cell death, suppress cancer development, and stop cancer metastasis. Antibiotic use not only disturbs the microbiome but also weakens the immune system and increases inflammation, which may affect and lessen the effectiveness of the treatment of cancer [163].

3.6.1. Daunomycin

An antibiotic called Daunomycin, commonly referred to as Daunorubicin, was isolated from the bacterial species *Streptomyces peucetius* [164, 165]. Anthracycline antibiotic, Daunorubicin, is usually utilized to treat different malignancies. It appears to be a glycoside that is soluble in organic solvents but insoluble in water. Acute non-lymphocytic leukemias in adults and acute lymphocytic leukemia (ALL) in both children and adults can be treated with Daunorubicin, an anti--neoplastic drug, in conjunction with another cytotoxic drug to induce remission. When administered alone, Daunorubicin hydrochloride has been shown to have a complete remission rate between 40 and 50 percent and between 53 and 65 percent when combined with cytarabine [166]. Ascites tumor is strongly inhibited by Daunomycin. Solid tumors exhibit lower sensitivity to Daunomycin than ascitic types [167].

3.6.1.1. Mechanism of Action

The mechanism of action of Daunomycin is that it damages the deoxyribonucleic acid. The damage to DNA is done due to intercalation between the base pairs, which causes the helix to uncoil and ultimately prevents DNA-dependent RNA synthesis and DNA synthesis. It may potentially work by altering the control of gene expression, producing free radicals, and inhibiting polymerase activity [168]. It interferes with DNA, DNA topoisomerase I and II, metal ions reactive oxygen species, and induces apoptosis, all of which contribute to its anti-cancer effects [169]. Daunorubicin's quinone structure enables it to function as an electron acceptor in activities carried out by oxo reductive enzymes, such as NADH dehydrogenase, cytochrome P450 reductase, and xanthine oxidase. Quinones become semiquinone free radicals when a free electron is added, and these radicals have the potential to damage DNA both directly and as a result of their interactions with molecules of oxygen to produce peroxides, superoxides, and hydroxyl radicals [170].

3.6.2. Bleomycin

Streptomyces verticillus produces a combination of cytotoxic glycopeptide antibiotics known as bleomycin

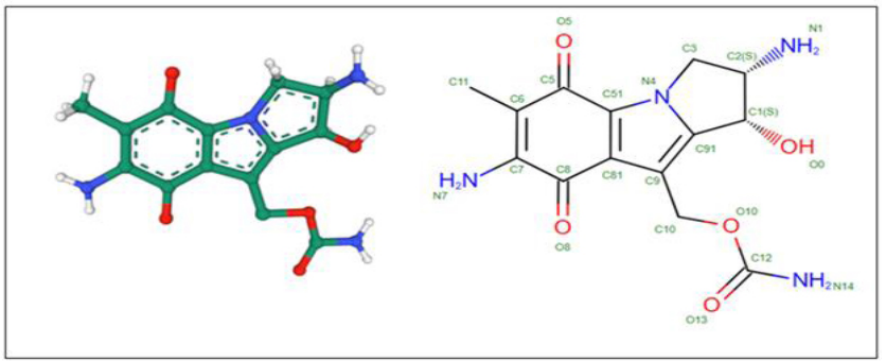

Fig. (10). The Linear Structure (2D view) of Mitomycin C from *Streptomyces caespitosus* (PDB ID: 1KLL). (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

(BLM). DNA is cleaved by bleomycin under the influence of oxygen and metal ions [171]. Under the presence of molecular oxygen, BLM binds DNA and Fe (I-I), releasing hydroxyl radicals that degrade DNA and oxidize Fe(II). BLM is used to treat ovarian cancer, malignant pleural effusion, testicular cancer, non-lymphoma, Hodgkin's disease, Hodgkin's head and squamous cell carcinoma of the neck [172]. The bleomycin structure is shown in Fig. (**9**).

3.6.2.1. Mechanism of Action

The main mode of action of bleomycin is its capacity to oxidatively damage deoxyribonucleic acid by attaching to metal ions, such as iron, and producing metallobleomycin complexes. These complexes produce reactive oxygen species, which break the 3'-4' bonds in deoxyribose to form double-strand and single-strand breaks in DNA. Freebase propenals, in particular thymine, are produced by these strand breaks. These free base propenals are known to cause cell cycle arrest at the G2 phase during synthesis. The progression of cell replication is stopped during this stage, which limits tissue growth and repair. After exposure to bleomycin, chromatid breaks and chromosomal abnormalities can be seen cytologically as a result of these effects [173].

3.6.3. Mitomycin C

Streptomyces caespitosus, a strain of actinomyces, is where mitomycin C was first discovered. By attaching to DNA along the process of alkylation, which causes the cross-linkage of double-helical DNA strands, this anti-cancer drug prevents DNA synthesis. The 2D structure of mitomycin is shown in Fig. (**10**). It expresses a protein called MRD for expressing resistance to the drug used. It is considered in the treatment of cancers of the lungs, anal, hepatic cell carcinoma, the head and neck, cervix, bladder, breast, colorectal and melanoma of the stomach, and melanoma of pancreatic cancer [174]. The linear structure of mitomycin C is illustrated in Fig. (**10**).

3.6.3.1. Mechanism of Action

Mitomycin is an agent that induces aneuploidy. By cross-linking guanine and cytosine, the anti-cancer antibiotic mitomycin-C specifically prevents the synthesis of DNA. DNA is cross-linked at the N6 position of adenine, the O6 position of guanine, and the N2 position of DNA by mitomycin C, which also suppresses DNA synthesis. In addition, reduced mitomycin C results in single-strand DNA breaks. Mitomycin that has been reduced inhibits DNA synthesis by producing oxygen radicals, alkylating DNA, and interstrand DNA cross-links. It works by first undergoing two one-electron reductions to the equivalent semiquinone and then to hydroquinone. Both forms can start a series of events, leading to DNA alkylation. At high concentrations, mitomycin C can prevent the synthesis of RNA and proteins [175].

3.6.4. Actinomycin D

Actinomyces antibioticus produces the well-known antibiotic actinomycin D (dactinomycin), which has antibacterial and anti-cancer properties. The cytotoxic and antitumor effects of actinomycin D are mediated by several different mechanisms, including intercalation to DNA, stability of cleavable topoisomerase I and II complexes with photodynamic activity, free radical production, and DNA. Ewing sarcoma, Wilms cancer, trophoblastic tumours, and neuroblastomas can all be successfully treated with actinomycin D, mainly in youngsters [176].

3.6.4.1. Mechanism of Action

A polypeptide antibiotic called actinomycin D (Act D) was discovered in the species Streptomyces. Act D intercalates into DNA and stops RNA polymerases from progression. It is a common transcription inhibitor. Act D in nanomolar doses inhibits RNA polymerase I transcription and causes nucleolar stress by interfering with ribosome synthesis. By inducing apoptosis, it exerts its effect. At the mitochondrial level, the intrinsic pathway or the extrinsic (receptor) pathway can initiate apoptosis. When TNFR superfamily members like TRAILR1, CD137, TNFR, R2, and FAS are activated, death domain proteins are recruited, and caspase-8 is activated. This can cause Bid to be cleaved and the intrinsic apoptotic pathway to be activated. When the TNFR superfamily is activated, NF-B, a crucial regulatory protein that can start cell death, is also activated. When combined with RG7787, actinomycin D triggers the extrinsic pathway of apoptosis, which kills several cancer cell types and results in dramatic tumor shrinkage in mice [177].

3.6.5. Doxorubicin

The bacteria *Streptomyces peucetius* is the source of the antibiotic Doxorubicin (DOX). Doxorubicin belongs to the class of chemotherapy drugs known as anthracyclines. Doxorubicin is frequently used as a medication in the treatment of solid tumors in both adult and paediatric patients. DOX affects the nucleic acid of dividing cells in two ways: (i) By intercalating between DNA base pairs and enabling the transcription replication processes in rapidly growing cells, and (ii) by having iron-mediated free radicals that enable damage to cellular membranes oxidatively, proteins, and DNA. It is used for various kinds of cancers, namely breast cancer, bone sarcoma, ovary cancer, and leukemia [53]. The FDA has given the liposomal doxorubicin formulation approval for the treatment of Kaposi sarcoma associated with AIDS, multiple myeloma, and ovarian cancer in patients who have failed platinum-based chemotherapy [178].

3.6.5.1. Mechanism of Action

The main method of action of doxorubicin is its capacity to intercalate among DNA base pairs, breaking DNA strands and inhibiting the synthesis of both DNA and RNA. By obstructing the topo isomerase 2 enzyme, it inhibits or prevents the development of cancer cells. This enzyme is required for cancer cell division and growth. It also inhibits the activation of apoptosis. Doxorubicin also results in free radical-mediated oxidative damage to DNA when paired with iron, severely restricting DNA synthesis. By restricting the binding of doxorubicin with iron, iron chelators like dexrazoxane may inhibit the production of free radicals [179]. Reactive oxygen species are produced when doxorubicin is oxidised to semiquinone, an unstable metabolite that is then transformed back into doxorubicin. Reactive oxygen species can cause DNA damage, oxidative stress, lipid peroxidation, and membrane damage, as well as start the apoptotic pathways that cause cell death. Alternatively, topoisomerase-II can be poisoned by doxorubicin as it enters the nucleus, which also causes DNA damage and cell death [180].

4. PROS AND CONS OF BACTERIAL PEPTIDES IN CANCER THERAPY

In recent years, antitumor bacterial strains have been extensively investigated as a unique method to treat cancer [181]. Bacterial anti-cancerous substances provide an effective alternative treatment for cancer. However, there are benefits and drawbacks to these cutting-edge cancer therapy options [182]. Some of the drawbacks include metabolic instability, rapid clearance, and high manufacturing costs. The main issue with bacteria or their respective agents is the toxicity that results at therapeutic dose levels [132, 183]. Another difficulty is incomplete tumor lysis, which occurs when bacteria do not always destroy the entire tumor, necessitating radiation or chemotherapy [132, 184]. In-depth research is required before using bacteria or bacterial agents to treat cancer due to biosafety concerns, the instability of toxin genes, and interactions with other therapy medications [185-187]. Fig. (**11**) shows the pros and cons of using bacterial peptides as anti-cancer agents.

5. CHALLENGES AND FUTURE PROSPECTS

The unique pathophysiology of different tumors of origin represents a major obstacle to current cancer therapy [188]. Microorganism's genetic flexibility, which enables fine-tuning, may be their greatest strength in tailored treatment against the cytotoxic effects of cancer [189]. Bacterial anti-cancerous substances provide an effective alternative treatment for cancer [190, 191]. The dramatic progress in the large-scale synthesis of peptides enables the production of peptide-based anti-cancer drugs at a more affordable price for patients [192]. The ethical use of microbial mechanisms and their tumor-targeting properties endorse vital, personalized applications because this kind of degree of control can be used for every patient's unique tumor type. One of the mechanisms is metagenomics, which acts like a weapon. This is used to

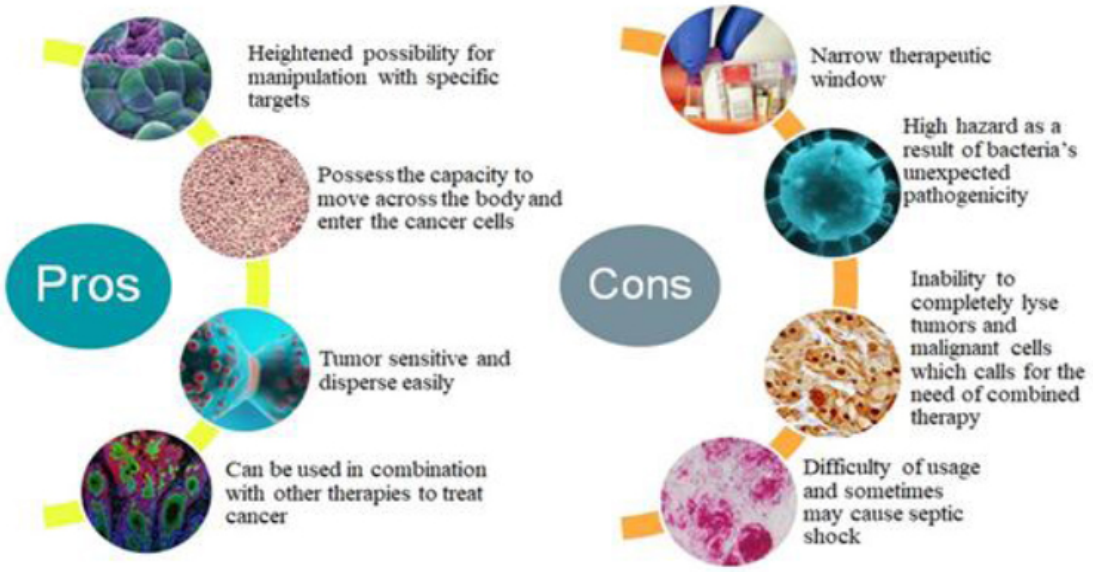

Fig. (11). Pros and cons of bacterial peptides as anti-cancer agents. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

know more about the communities of microbes [193]. It refers to DNA extraction from a community where the genomes of all the different organisms present in the community are pooled up [194]. The metagenomics approach has paved the way for treating diseases in a much more efficient way. Metagenomics has led to the complete sequencing of pathogenic and useful microbes. DNA extraction and cloning are done from all the genomes of microorganisms, collected specifically from soil type or water type. Cancer has been linked to the gut microbiota, and studies have shown that it can affect how well anticancer drugs work. Changes in the gut microbiota have been linked to immune checkpoint inhibitors (ICIs) or chemotherapy treatment resistance, whereas the addition of specific bacterial species improves the effectiveness of anticancer medications [195]. When these microbiota were taken and sequenced, they showed promising results of enzymatic activity and antibiotic action against cancer. Thus, there has been a surge in the number of chemicals obtained from microbiota in pre-clinical or clinical studies for treating tumours. Different species of facultative anaerobic bacteria and obligate bacteria can mostly target cancer cells growing in hypoxic regions of solid tumors. Bacterial proteins can usually enter cancer cells and interfere with or kill cancer cell growth through multiple mechanisms [196]. Due to bacteria's selective cytotoxicity, responsiveness to external signals, high specificity against cancer cells, control after ingesting bioengineered bacteria, and their therapeutic properties have surpassed the limitations of existing cancer therapies and proven to be the most suitable methods in treating cancer [197]. Bioengineering of bacteriocins may provide a possibility to increase the potency of naturally occurring bacteriocins by creating hybrid bacteriocins with the necessary properties [198]. As a single anti-cancer agent is not so suitable for treatment due to its heterogeneity, the data present strongly supports the idea of combining conventional therapies with immunotherapy, *e.g.*, radiation and chemotherapy, thus improving efficacy in cancer treatment and management. This promotes a synergetic effect, providing a new avenue for cancer treatment. Some studies also proved that gut bacteria can be helpful in the process of carcinogenesis. Therefore, these kinds of bacteriocins show the dual activity of both antimicrobial and anti-cancer properties [199]. More rigorous research needs to be done to overcome the restrictions and adverse effects of bacteriotherapy as the field of bacterial-based cancer therapy (BBCT) is still regarded as being fairly novel, and it has the potential to be considered further as it has provided promising results in some of the *in vitro* and *in vivo* studies conducted leading to clinical trials [200]. Therefore, to learn more about the efficacy of BBCT, the scientific and clinical community must start planning further clinical trials leading to promising results and fighting back against cancer [201].

CONCLUSION

Host defense peptides and proteins evolved throughout evolution in varying organisms, including fungi, animals, bacteria, humans, and plants. Some compounds, such as those with antibacterial and anti-cancer activities, display multifunctional activity. However, there are only a limited number of these bioactive chemicals that have been discovered so far. An increasingly popular class of anti-cancer medicines is bacterial peptides. In the current review, some of the bacterial peptides with anti-cancer properties have been discussed. They are distinguished by hydrophobicity and low molecular weight. These properties appear to be crucial for the penetration stage of these peptides into tumor cells. There is hope for the pharmacological application of several of these peptides in the treatment of oncogenesis as they are under clinical development. In conclusion, bacteria are a valuable but little-known source of physiologically active compounds, such as anti-cancer proteins and peptides. Several anti-cancer bacterial proteins/peptides are approved by the FDA for usage, like doxorubicin, bleomycin, futibatinib, *etc.* Apart from these, various other bacterial peptides are still undergoing clinical trials, such as methionase and arginine deiminase. Hence, there is a need for more research in this direction for these bacterial peptides to be used as anti-cancer agents.

CONSENT FOR PUBLICATION

All authors have read the final version of the manuscript and approved it for publication.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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REVIEW ARTICLE

Food Contamination with Micro-plastics: Occurrences, Bioavailability, Human Vulnerability, and Prevention

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Abstract: Microplastics (MPs) are emergent environmental contaminants that are designated as either primary or secondary dependent on their origins. Formulation, morphology, dimensions, and colour scheme, along with other features, are connected with their propensity to reach the food webs and their dangers. Whilst ecological adversities of MPs have drawn considerable interest, the hazards to individuals from dietary exposure have yet to be determined. The aim of this review is to gauge existing understanding concerning MPs in foodstuffs and to explore the problems and inadequacies for threat assessment. The prevalence of MPs in foodstuffs and sugary drinks has been detected all over the world, but most researchers judged the existing information to be not only inadequate but also of dubious value, owing to the notable lack of agreement on a regulated quantification methods and a consistent appellation. Most published papers have highlighted potable water and condiments such as sugars, salts, and nectar as significant food components of MPs for humans. The threat assessment reveals significant discrepancies in our understanding of MP toxicity for human consumption, which hinders the estimate of risk-based regulations regarding food safety. The lack of comparators for evaluating MPs food consumption prohibits dietary MPs risk description and risk mitigation. Researchers and Food Safety Administrators confer various obstacles along with possibilities linked to the appearance of MPs in foodstuffs. Further investigation on the MPs categorization and exposures is essential considering that any subsequent threat evaluation record can contain a comprehensive dietary viewpoint.

Keywords: Food contamination, food safety, human vulnerability, microplastics, toxicity.

1. INTRODUCTION

Microplastics (MPs) were reported as rising ecological contaminants, particularly those damaging the marine ecology, but they ought to be regarded as a developing culinary pollutant. Annually, about 5 and 13 tonnes of plastic (1.5-4% of estimated worldwide output) enter aquatic habitats [1]. MPs are also posing a rising threat to terrestrial ecosystems, as they have been found in farmland sites [2]. Lately, COVID-19 virus protection efforts have resulted in a rise in plastic treatment and disposal, as safety clothes, accouterments, face masks, and supplementary plastic commodities and plastic packaging are fixed consumption [3]. Primary MPs are designed to be purposefully introduced to consumer applications like toiletries and clothing materials. These result in a minor portion of the overall amount of MPs found in the aquatic bodies, but sewerage has been designated as the prime radix since treatment mechanisms do not appear to be capable of removing them. The avoidance of primary MPs' ecological consequences is straightforward. In actuality, the EU has begun a program to restrict the utilization of these compounds, in line with the guidelines of the European Chemical Agency (ECHA), and enterprises have taken voluntary transactions in this direction [4]. In January 2019, ECHA suggested wide range of limitations regarding the utilization of MPs in commodities sold in the EU in order to reduce their environmental impact. Several possibilities are being considered by the EC as an aspect of its polymer policy and the emerging corporate sustainability action plan. Secondary MPs are constituted of the disintegration of bulk materials when subjected to ultraviolet radiation, thermal decomposition, heated oxidative deterioration, mechanical erosion, microbial degradation, and hydrolysis. Secondary MPs can materialize from multiple semblances, like fishing, gear, sludge, plastic containers, wrappers, industrial debris, fabrics, and rubber. Polymers used to make MPs include polyethylene (PE), polyurethane (PU), polypropylene (PP), polyvinyl chloride (PVC), polystyrene (PS), and polyethylene terephthalate (PET) [5]. Furthermore, the emergence of novel polymers like Tritan that seek to solve many technical difficulties must be investigated during subsequent study since their usage is projected to expand. Additionally, the topology of MPs particles is extremely variable, encompassing yarns, microbeads, coatings, foams, granules, and so

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on [6]. MPs conformation, ample supply, dimension, and thickness, along with other characteristics, might influence the bio susceptibility of MPs absorption by zooplankton and hence both the biomagnification cycle and the translocation across taxonomic groups in the aquatic ecosystems [7]. According to existing research, majority of marine creatures are in danger of interacting with MPs [8]. Polymers, combined with wastewater, can directly access aquatic ecosystems [9]. As a consequence of kinetic demand, UV vulnerability, weather patterns, tidal influences, and physiological structures, these materials can remain in water sources or disintegrate into smaller components [10]. These MPs can account for almost 95% of aquatic debris, which accumulates and spreads throughout water ecosystem modules, freshwater habitats and water streams, coastal waters, shoreline, oceanic beds, and even inside aquatic organisms, and exhibit significant dimensional and corporeal changes [11, 12]. MPs infiltrate aquatic habitats by sewage, air currents, and wave cycles, placing life forms in danger owing to ingestion [13]. Whilst ecological impact of MPs has garnered considerable interest among researchers, policymakers, and the public as a whole, the health hazard resulting from the ingestion of contaminated MPs has yet to be studied [14]. There is a continuous and substantial lack of awareness about the key concern additives utilized by the plastic industry, microplastics discharged into the ecosystem, and their subsequent consequences on people's wellbeing [15].

An investigation team summarized in 2019 that, notwithstanding mounting proofs that MPs pollute a wide range of foods and liquid refreshments, as well as both indoor and outdoor surroundings, and the likelihood of adverse health outcomes resulting from the consumption and/or respiration, an inquiry was warranted [16]. Although the majority of MPs ingested are eliminated (>90%), only molecules lesser than 150 microns can migrate across the gastrointestinal epithelium and pose risks [17]. Unfortunately, there is a significant research vacuum pertaining to the MPs' risk to health. There is possible immunotoxicity past immunosuppression and immunological functionalization, alteration of oxidative stress regulation token of genes, and stimulation of the E2 (Nrf) nuclear factor translation, amidst other things [18]. Organizations such as the European Food Safety Authority (EFSA) and the Spanish Food Safety and Nutrition Agency (AESAN), and others, agree that the present scientism and information do not provide a robust sufficient foundation for evaluating the danger of MPs [2]. The raising understanding of this issue has resulted in various programmes and policies, like Imptox, Plasticsfate, Plasticsheal, and Polyrisk, regardless of the European Horizon 2020 programme. Because MPs provide possible health concerns when consumed, the existence of MPs in foodstuffs and the volume of dietary consumption should be examined. As a result, the grail of this review is not just to critique existing understanding, gaping holes, and problems concerning dietary MPs, but also to analyze them for oral ingestion from their primary dietary sources.

The aim of this review is to gauge existing understanding concerning MPs in foodstuffs and to explore the problems and inadequacies for threat assessment. The prevalence of MPs in foodstuffs and sugary drinks has been detected all over the world, but most researchers judged the existing information to be not only inadequate but also of dubious value, owing to the notable lack of agreement on a regulated quantification methods and a consistent appellation.

2. CHARACTERIZATION OF MP'S

In aquatic media, microplastics can come in a variety of dimensions, forms, and tints. The distinction between primary and secondary microplastics is the fundamental one. Secondary microplastics, which are by-products of deterioration and deposition, more frequently have an amorphous shape than primary microplastics, which are commercially generated particles with a uniform, typically globular, or filamentous shape with a homogeneous surface. Yet, it is accurate that weathering can drastically change both varieties of microplastics [19]. The methods used for testing and processing determine the dimension of the microplastics found in sediments or waters. Particles >500 m are preserved in a mesh sieve and can be grouped employing a dissecting (stereo) microscope. According to a study [20], there is a contrast in the technique for the detection and measurement of microplastics from the aquatic environments in 68 analyses, while particles 500 m are typically only procured by research employing density separation and filtration. The researchers additionally suggested classifying the collected microplastics into 5 mm–500 micron and 500-micron size ranges. Due to recovery inefficiencies and mistakes in differentiating microplastics from particles of biological sources, the collection of the tiniest portions of microplastics is the most challenging. The diameter of the microplastics is also important for their progression in the animal food chain because smaller microplastics are easier for some organisms to reach, like planktonic lifeforms [21]. Granules, pieces, and fibres are the forms of microplastics that are most frequently recorded, with coatings, cables, strands, sponges, elastomers, latex, and microbeads (in decreasing order) all playing a potential function in the pollution caused by microplastics [22]. Microplastics come in a plethora of colours with different sizes and shapes. Blue, white, transparent, black, red, and green are the most prevalent hues. The "multicolor" colour is one example since some microplastics can have various hues on disparate sections. Moreover, hues like purple, yellow, brown, pink, and others are present but in much smaller amounts [23]. Because a few entities are known to significantly consume microplastics depending on a colour predilection behavior, color is relevant for investigations involving marine animals. Moreover, color can reveal how heavily polluted with toxins microplastics are. Clear and white microplastics are the most frequently ingested by aquatic creatures, while yellow and black microplastics are among those bulk poisoned by long-lasting biological contaminants [19]. White, pale yellow, and cream microplastics are the most frequently mentioned in the records [20]. Although white and matte microplastics are frequently produced from PE and low-density polyethylene (LDPE), while clear and translucent microplastics are frequently formed by

PP, the colour of the microplastics may also be utilized to determine the kind of polymer [24].

3. DIRECT AND INDIRECT OCCURRENCE OF MICROPLASTICS IN FOOD AND BEVERAGES

Microplastics may build up in an individual's system through a variety of exposure levels, including particle aspiration and direct eating of microplastic-contaminated food. In reality, the maximum projected microplastic concentrations from grime consumption for elders and youngsters are approximately 1000 and 3000 particles annually, accordingly. At the moment, we know very little about the impacts and cytotoxicity of microplastics on humans, and studying the fortifying movement of microplastics in the food chain to individuals is vital for avoiding microplastic pollution [25]. As mentioned before, microplastics can be produced using an array of methods and transferred over several environmental media, ultimately hitting the food chain and, lastly, the human body. Human intake of tainted beverages and food is a problem, even though it appears to be underappreciated in comparison to ecological impact. To prevent massive mistakes in the conclusions, beverages and food samples must be extensively analyzed before marketing [26].

3.1. Packaged Food

Plastic containers are currently commonly employed for food packing and takeaway service, and thus may be a significant source of MPs consumed by individuals. As a result, it is critical to investigate the MPs produced by plastic canisters during this operation. It was discovered that plastic MPs and Nanoparticles (NPs) were present in the cup after immersing empty plastic tea sachets in RO water for a period of five minutes at 95°C. The research revealed that 11.6 billion MPs and 3.1 billion NPs were found in just one cup, all of which originated from plastic sachets, with particle sizes ranging from 520 nm to 270 m. MPs are discovered in two distinct instances in packaged food. The primordial origin is food casseroles, which are frequently composed of extruded polystyrene (XPS) [27]. When you open the package, you will generate a second source of MPs. In another study [28], the MPs produced in the course of plastic package perforations were reviewed. Depending on the stiffness, thickness, concentration of plastic substance and expanse of MPs, these techniques could create 0.46-250 MPs/cm.

The evaluation of MPs levels in commonly consumed fruits and vegetables is absolutely essential. Another study [29] investigated the quantity and dimensions of MPs in frequently edible fruits and vegetables (B. oleracea, Lactuca sativa, Daucus carota, and Solanum tuberosum, Malus domestica, Pyrus communis). Of the various specimens, apples (Malus domestica) constituted the most polluted fruit, whereas carrots constituted the bulk of infested vegetables. Salads, like lettuce, in contrast, were the lightest tainted group. Plastic pieces were found in higher concentrations in fruits than in vegetable consumable components, according to the findings. MPs can enter plant cells through the seeds, roots, rhizome, foliage, and fruits. Apart from the significant vasculature of the fruit extract, the dimensions and complexity of the rhizosphere, as well as the maturity of the plants, were factors that resulted in more MPs in fruits than vegetables. Furthermore, food addons may be prime determinants of MPs that penetrate marine diets. MPs are said to comprise 4% of culinary addons on median [30]. Moreover, stabilizers, colouring agents, coolants, coagulants, acidifiers, as well as other dietary addons are commonly employed in oceanic cuisine. Three carotenoids, viz. haematite and two different types of PB (Pigment Blue) (PB 15:1 and PB 15:3), were found in two commercially accessible aquatic species (M. edulis and Crassostrea gigas), demonstrating that various types of dietary enhancers progressively spread into freshwater ecosystems *via* the MPs. It consequently suggests that food addiction can be hazardous to the nutritional value and security of aquatic products, as well as establishing powerful avenues for MPs [31].

3.2. Retail Drinking Water

MPs have been discovered in both ordinary and mineral water. Human - caused detritus was discovered in 81% of the 159 investigated specimens through an examination of potable water in 14 nations, with a composite rating of 5.45 particles/L [32]. Some research groups evaluated 11 universally procured labels of mineral water procured from 19 different places across nine different nations [33]. The analysis indicated that 93% of the 259 mineral water samples tested positive for MPs infiltration, with MPs sizes spanning from 6.5 to 100 m. Within mineral water, tiny bits were the most prevalent particle profile (65%). The distribution of particle sizes observed in water for consumption primarily focused on the 1-100 m band [34]. The conduit transports tapped water towards the water usage section once it's been treated over several operations in the drinking water treatment plant (DWTP). As a result, the MPs in water from the tap are primarily derived from crude water and the treatment and distribution processes. MPs in crude water are mostly caused by the disintegration of numerous polymeric entities and the emission of residential eluent [34]. Also, to avoid rusting, the storage facilities of DWTPs are covered with epoxy coating. The conveyance pipelines are typically composed of PVC or PE, while the fixtures are constructed of PA [35]. MPs are also produced as a result of plastic erosion over transit and storage. The plastic concentration of bottled water may be affected by the product packaging material [36]. The bulk prevalent composite identified (at least 54% of these bigger MPs) is polypropylene, which may be obtained through standard polymer designed to manufacture bottle seals [33]. Furthermore, components for packing were classified as one-way plastic water bottles, refundable plastic water bottles, glass containers, and soft drink packages [37].

The typical concentration of polymeric waste in water from refundable bottles (118 particles/L) was substantially greater than in water from solitary plastic bottles (14 particles/L) and soft drink packages (11 particles/L). Nonetheless, a vast proportion of MPs were discovered in glass bottle water (average number: 50). This problem might well be triggered by the bottle lid and sealant creating auxiliary abra-

sion upon the soft plastic substance. Other than exfoliation, MPs can also be generated through the polishing of glass canisters. Furthermore, fluorescence microscopy demonstrated that when disposable paper cups utilized, roughly 25,000 μm-diameter microplastic granules were discharged into a hot water cup (100 ml) within 15 minutes [38].

3.3. Retail Beverages

In essence, the liquid refreshments market requires a large amount of clean water for manufacturing and purification, and water is the major contributor of MPs in sugary drinks [39]. The components used in the manufacturing process are a second viable cause of pollutant ingestion into beverages. Because beverages may come into direct contact with vacuum of space during the manufacturing procedure, the subsequent apportion of MPs in sugary drinks is the environment. Aiding to the aforementioned problems, the procurements and machinery utilized in the manufacturing process (mostly filters) might pollute the environment [40, 39, 41]. Several investigations looked into the pollution of sweetened drinks with MPs [39]. Dealers in breweries have garnered a great deal of interest.

A group of investigators recently studied a variety of beverages, such as sugary beverages, energy fluids, and cold tea. Furthermore, only fibres were found in the three examined beverages, with blue fibres dominating, next after brown (apart from energy drinks) and red fibres [39]. It was discovered that MPs elements <1000 μm constitute for the biggest amount for the three products. Milk and cheese products are among the multinational essentials for steady profit; international production grew to 75 million tonnes (in dairy product analogues), and global milk production was projected to be 843 million tonnes in 2018 [42]. (FAO 2019). Yet, in order to promote hygiene and public health, the commercial procedure of milk supply has been impacted by multiple technical innovations, which have altered milk formulation. Given the extensive refining of milk, there is a risk of microplastic pollution of milk from poor cleanliness procedural machinery, the environmental elements, water system constraints, and insufficient milk management.

MPs were found in dairy milk commodities in Mexico, where 23 milk samples from 5 international and 3 national brands were tested. Microplastics were found in all of the samples tested. The morphological properties and configurational content of microplastics in milk specimens were investigated using scanning electron microscopy supplemented with energy-dispersive X-ray spectroscopy (SEM-EDS). The thermoplastic sulfone plastics used in ultrafiltration and microfiltration screens in the food and dairy industries are the higher pervading pollutants identified in milk samples. Excessive pressure and continual biochemical and physical exertion might destroy the films, ripping off granules from filter media and potentially contaminating fluid milk samples with microplastics. The discharge of microplastics from milk poses severe threats because new-borns are the primary users of milk. As demonstrated in the paper, infant feeding bottles, which are usually composed of PP, can introduce microplastics into milk [43].

3.4. Indirect Occurrence in Food Chain

In parallel to the foods mentioned previously, a handful of studies on MPs in additional foods, such as salts, sugars, and honey, were also reviewed. Some researchers have discovered MPs infestation in five Swiss honey samples [44]. Black granules, white transparent fibres, white transparent particles, coloured fibres, and colourful particles are all present. Despite the fact that MPs were identified in all kinds of honey tested, the authors concluded that there was no indication that polymeric pieces of plastic were carried straightforwardly from flowers into the beehive and nectar by honeybees. The MPs discovered were linked to beekeepers' activity. Scientists also discerned 19 honey illustratives from five countries and discovered that fibres and tiny pieces were hitherto prevalent in the bees' fodder and are transmitted from the flowers to the beehives by the pests, resulting in a diametric opposition to the observations [44]. Further investigation is required to verify the origins of MPs in nectar. The Swiss Beekeepers Association initiated additional research in 2019 to determine the source of MP pollution in nectar. As a result, they distinguished between beehives constructed of wood and those composed of polystyrene in order to investigate the important pollution element in honey. They were successful in determining the constituent elements for these component types using attenuated total reflection--Fourier transform infrared spectroscopy (ATR-FTIR) as well as Raman techniques, which enabled them to trace the particles to their precise provenance under certain instances. The findings show no proof of significant infiltrations in nectar from natural origins; however, some microscopic particles may be linked to beekeeping practices [44]. Microplastics have also been found in Ecuadorian nectar, with accumulations of 54 and 67 particles/L in commercial and handmade honey, accordingly. This microplastic pollution of food stuffs was most likely caused by air input amid manufacturing procedures [45]. The average microplastic particles concentrations in sugar (except beet sugar) were around 217 fibers/kg and 32 fragments/kg, with highest of 388 and 270, correspondingly. There was no variation between vibrant and translucent particles in these samples. Foreign sugar providers typically offer purities higher than 99.8%, with these sugars containing no more than 0.2% foreign matter. Considering the substantial number of foreign particles identified in nectar and sugars, they are unlikely to surpass any regulatory or corporate limitations.

Much research on the microplastic pollution of salt destined for human intake has been reported and debated in recent years. Salts offer key nutritional components and are employed in food storage techniques due to their chemical properties and low affordability (*e.g.*, fruits, cheese, cereals, and drinks). Additional applications for salt include the personal hygiene and cosmetic product industries, as well as the medical business (as an additive, emulsifier, and binder) [46]. Cellophane (CPH), polyethylene-vinyl acetate (PE-VA), PA, polyacrylonitrile (PAN), polyalkene, po-

ly(1-butene), PET, poly(metylacrylate), PP, phenoxy resin (PR), polyurethane (PU), polyvinyl chloride (PVC), and paraffin wax were among the particles found in sea salt. As a result, the maximum annual human vulnerability is calculated to be 6110 microplastic fragments, corroborating salt.

4. BIOAVAILABILITY FOR HUMANS

Microplastics enter the human body by several methods, including ingesting [39], inhaling [47], and absorbed through the skin [48]. Each one of these exposure pathways is linked to certain surroundings and its chemical-physical properties. MPs have the ability to harm individual wellness through inflammatory response and subsequent genotoxicity, and their buildup can trigger or increase an immune reaction [49].

4.1. Ingestion

One of the most common ways of entry for MPs and NPs is ingestion (oral intake) [12]. Like other nonbiological micro- and nanoparticles, aspirated microplastics can enter the pulmonary membranes by diffusing, direct cellular infiltration, or dynamic cellular uptake [26]. The first consequences of microplastic aspiration were evaluated in plastic processing employees. Histopathological examination of the employees' lungs revealed interstitial fibrosis and granulomatous tumors, which were thought to be caused by acrylic, polyester, and nylon dust [50]. The proportion of microplastic particles accumulated by inhaling against ingesting (through the food chain) has also been reported in research. It was discovered that the amount of MPs inhaled was 3 to 15 times more than the amount swallowed, implying that human MP intake is modest when contrasted to exposures [51].

4.2. Inhalation

The next major source of exposure for MPs and NPs is aspiration (breathing) [52]. MPs and NPs have been identified in the surrounding atmosphere [52, 53]. Yet, owing to their diminutive acreage, environmental MPs and NPs can be readily uptaken and present human health problems by collecting in the respiratory system and eventually breaching the blood-brain barrier (BBB) [52]. MP fibres with diameters of more than 250 m were discovered in human lung tissue [54]. In the immediate and long-term, the elemental makeup of these particles may induce both immediate and ongoing breathing difficulties. Several fibrous MPs could well be aspirated, and the bulk is eliminated through mucosal cell filteration; nonetheless, a few could stay in the lungs, eliciting a localised physiological predisposition involving inflammatory reaction, especially in those with poor clearing mechanisms [49]. An experiment using a Breathing Thermal Manikin (BTM) to mimic human contact with aerial microplastics discovered that MPs could be ingested as a result of possible immediate human vulnerability to microplastic debris *via* air conditioning systems [55]. A research group recently revealed that inhaling polystyrene MPs/NPs exacerbated irritation and the activation of the inflammatory proteins (TGF-) and TNF- in lung tissue [56]. More research is required to establish contact and absorption rates in both interior and exterior scenarios in order to adequately analyze the hazard of such MPs and NPs. Furthermore, examining MP lung exposure pathways in humans might be a humanitarian difficulty as well as a methodological rigor issue. Several environmental factors influence MP transmission in the atmosphere, including airspeed, initial concentration, and air movement.

The MPs found in the atmosphere and smog were predominantly polyethylene (PE), polystyrene (PS), polyethylene terephthalate (PET), and other fibres of diameters ranging from 10-8000 m [57].

4.3. Dermal Contact

Cutaneous interaction with microplastics is regarded as a barely prominent way to be exposed, typically connected with vulnerability to monomers and admixtures, such as the endocrine toxicants bisphenol A and phthalates, from home accessories [48]. Epidermal absorbance, for example, was studied in rainbow trout. There is confirmation of 1-micron latex ball uptake from the aquatic environment, with granules positioning and remaining in the skin's interface and sub-surface epithelia, as well as phagocytic cells underneath the gill membrane. In humans, laparoscopic apparatus, such as braided polyester and polypropylene, are known to cause modest neuroinflammation as well as a foreign body syndrome with fibrous entrapment. Furthermore, access to microplastics and nanoplastics triggers oxidative stress in human epithelial cells [58]. Microplastics in consumption goods such as skincare products and cleansers can add to the danger of polyethylene MP exposure. These very consumer goods might contain acrylic ingredients, which may trigger allergic reactions with chemicals in our body's epoxy resin system [59]. Furthermore, reception *via* the epidermis is unlikely due to the physical and chemical features of MPs and the notion that nanoparticle assimilation across the dermis requires perforation of the stratum corneum, which is constrained to fragments smaller than 10 and 100 nm. Yet, several other research believed that NPs could infiltrate the surface of the skin [60]. Moreover, the prospect of MPs being exposed to air dispersion as percutaneous contamination involving accumulation on the skin has previously been described. This shows that MPs and NPs in individuals might not always permeate the subtler layers of skin, but may lodge on the papillary dermis. Encounter with MPs/NPs with surface-adsorbed synthetic substances, on the other hand, may lead to inflammation and increased retention. As a result, it is vital to research the potentially harmful consequences of nanoplastics and significant dermal contact with microplastics (for example, from grime, microbeads, and fluidic hand-washers) (Fig. **1** and **2**), (Table **1** and **2**).

5. HUMAN VULNERABILITY

Human beings are prone to MPs/NPs by ingesting, inhaling, and skin interaction, which can have negative health effects. Current study has presented persuasive evidence that MPs/NPs are potentially harmful to people [73, 74]. Phthalates, bisphenol A (BPA), bromine-based flame retardants

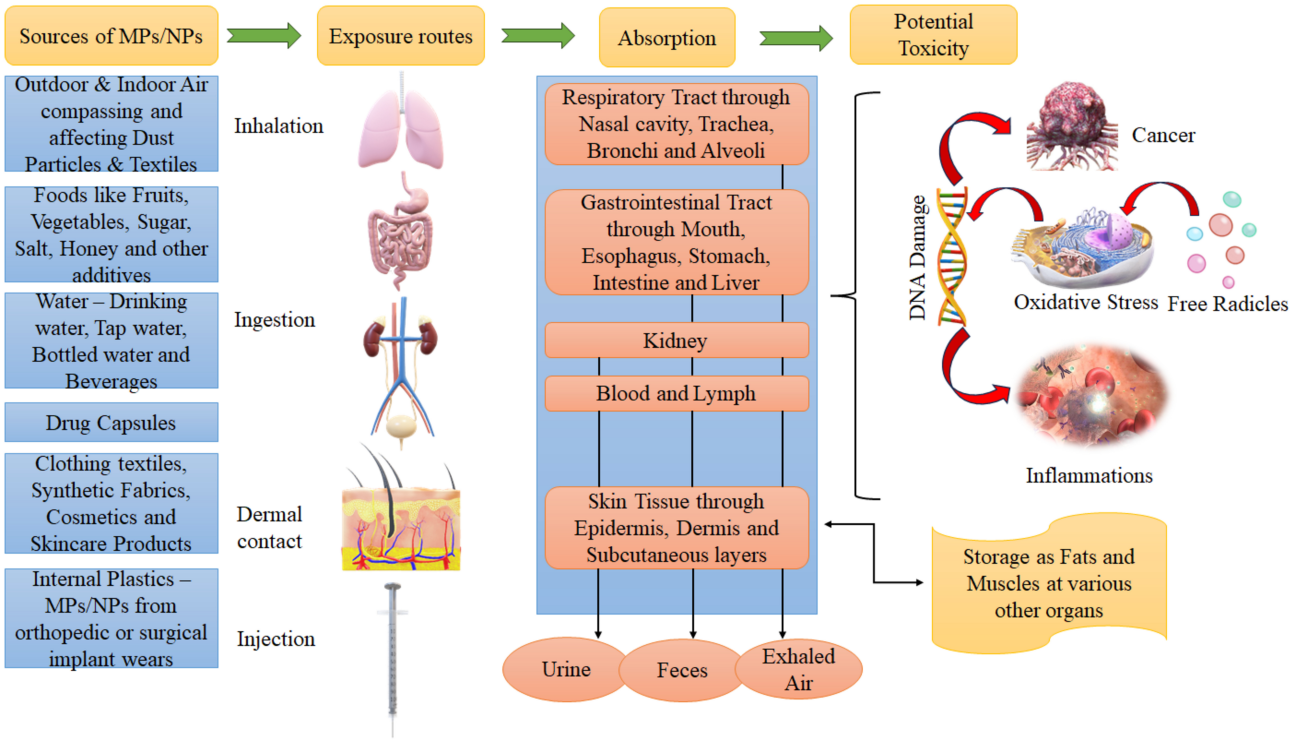

Fig. (1). Possible pathways and routes of exposure to MPs/NPs and potential toxic effects on humans. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

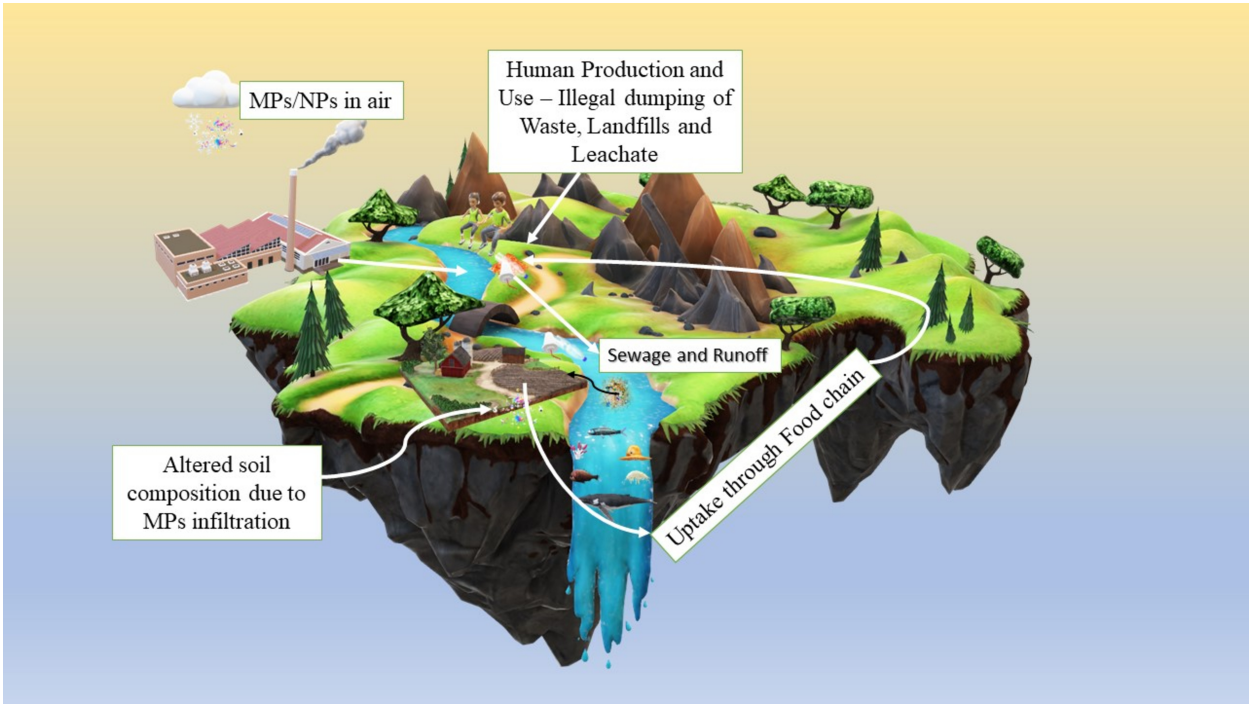

Fig. (2). Microplastic tailored pollution and consequent entry into food chain. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Table 1. Exposure assessments to microplastics through various individual sources.

Source of Exposure	Estimated Consumption	Exposure Level	Type of Polymer	References
Water and beverages	2.2-3 L/day	4400-5800 particles/ person/ Year	Anthropogenic debris	[32]
Bottled mineral water	2 L/day (adults) 1L/day (children)	1,531,524 particles/kg/ body weight/day (adults) 3,350,208 particles/kg/ body weight/day (children)	PET	[61]
Salts	14.8-18.01 g/day	Up to 302 particles/person/year	PE, PP, PET, PU, PVC, PA	[62]
Fruit and vegetables	High intake of apples and pears of 165.3 and 115.7 g/ day for adults and children, respectively Low intake for carrots of 20.3 and 18.0 g/day for adults and children, respectively	1.15 × 105- 1.41 × 106 particles/ kg body weight /day (children) 2.96 × 104- 4.62 × 105 particles/ kg body weigh /day (adults)	Not reported	[29]
Seafood	9.6 -57 kg/year	518 – 3078 particles/person/ Year	PE, polyester, semisynthetic Cellulose	[63]
Vinegar	3.1 L/year	Up to 3.68 particles/kg/body weight/year (adults) Up to 16.08 particles/kg/body weight/year (children)	PE, butylated hydroxytoluene, Irganox, Erucamide	[64]
Food contact materials	4-7 takeouts weekly	12–203 particles/person/weekly	PP, PS, PE, PET	[65]
Infant feeding bottles	-	14,600–4,550,000 particles/ person/day	PP	[43]
Household dust fallout	Evening meals	13,731-68,415 particles/person/ Year	Not applicable	[51]

Table 2. Summary of studies investigating the impact of MNPs on gut microbiota.

Biological Models	Micro/Nano Plastics (MNPs) Source	Polymer Type	Shape	Exposure Concentration	Results	References
***In vitro* digestion and simulation**	Pure PET pellets; blade milled to obtain MNPs	PET	Irregular	0.166g/intake	Modified microbial colonic community composition	[66]
In vitro	Powder purchased from local stores	PE	Spherical	0,100,1000 mg/L for 48hrs	Interaction with gut microbiota resulted in increased proportion of Clostridium, Bacteroides and Escherichia	[67]
***In vivo* mice model**	Procured from Polysciences.	PS	Spherical	0,0.2,1 or 10mg/Kg for 30 days	Oral exposure to PS MNPs accounted for the alteration of community	[68]
***In vivo* mice model**	Pristine carboxyl-modified and amino- modified were purchased from BaseLine ChromTech Research Centre.	PS	Spherical	0, 2, 0.2, mg/kg for 28 days	Oral administration of these MNPs resulted in marked gut microbiota dysbiosis.	[69]
***In vivo* mice model**	Clear PE microplastics were purchased from the Cospheric Company.	PE	Not mentioned	6, 60, and 600 mg/day for 5 weeks.	MNPs affected the composition and diversity of gut microbiota.	[70]
***In vivo* mice model**	Pristine and fluorescent polystyrene was purchased from Microspheres-Nanospheres.	PS	Not Mentioned	1.456 × 106 particles/L, 1.456 × 107 particles/L for six weeks.	The diversity of gut microbiota was altered after polystyrene MNP exposure. MNPs accumulated in the gut of mice and induced intestinal barrier dysfunction, gut microbiota dysbiosis, bile acids metabolism disorder in mice.	[71]
***In vivo* mice model**	Purchased from Microspheres-Nanospheres.	PS	Not Mentioned	1000 μg/L	MNPs induced gut microbiota; decreased the secretion of mucin in gut; induced hepatic lipid metabolism disorder in mice.	[72]

(BFR), triclosan, bisphenone, and organotins are examples of poisonous admixtures in plastic that are a real risk for public health. Polybrominated diphenyl ethers (PBDEs) are fire reducers employed in a variety of commercial applications. Plastics can contain up to 15% PBDEs, and because they are not additively bonded, they are prone to drain in the course of manufacturing, removal, and repurposing operations [75]. PBDE levels in both people and wildlife have increased over time, with the long-term implications uncertain [76]. A few investigations have suggested that biomagnification may result in altered brain maturation [77, 78] and neuroendocrine dysregulation [79].

5.1. Gastrointestinal and Urinary Tract Systems

Earlier studies investigated the migration of different types and measurements of MPs into the lymphatic vessels through the mammalian stomach, spanning from 0.1 to 150 m, and it has been demonstrated in human studies that the MPs may transit to the circulatory vessels [80]. It was revealed that both MPs and NPs-PS can cause oxidative stress in human epithelial cells *in vivo* [58]. Furthermore, studies on the abdomen of mice exposed to PS and PS (0.5 and 50 m) demonstrated a reduction in gastrointestinal secretion, as well as damage to the gut mucosal functionality and biochemical implications. One more study of human gastrointestinal cells subjected to PS and NPs *in vivo* revealed histopathological and proinflammatory responses; hence, NPs confirmed biocompatibility and induced death in all cell types [81]. Furthermore, regardless of the lack of anatomically perceptible abscesses and immune reactions, an investigation on human gastrointestinal epithelial cell lines Caco-2 and sourced co-cultures emulating gut M-cell/goblet cells by varying diameters of globular fluorescent polystyrene particles (1, 4, and 10 m) post *in vivo* exposure demonstrated a possible consequence on gut lymphocytes [82]. PS-NPs also altered cell survival and provocative gene function, cell etiology was highly stimulated, and there was a significant aggravation of IL-6 and IL-8 proteins in cells with gastric cancer [83], which can induce autoimmune destruction [84]. Human renal cortical epithelial (HRCE) cells treated with 44 nm polystyrene nanoparticles in the experiment indicated that NPs penetrated HRCE cells by a variety of pathways, both energy-liable (endocytosis) and energy-independent of kidney [85]. Furthermore, an *in vitro* human digestive model study discovered that microplastics produced more Cr than groundwater. Although the gastrointestinal stage producing the most bioavailable hexavalent chromium (Cr^{+6}), trivalent chromium (Cr^{+3}) may pose larger non-carcinogenic risks for human beings [86]. As a result, it gathered data from an evaluation of both *in vitro* and *in vivo* investigations. It could first confirm that contact with MPs and NPs in the internal organs *via* the abdomen can exacerbate cell membrane aggravation. Unfortunately, at this moment, nothing is established overviewing the impacts of these MPs and NPs on people's well-being. As a result, more investigation on exposure in experimental specimens and human cells is needed.

5.2. Respiratory Tract System

In advanced vertebrates, the respiratory system is an essential part of oxygen transport and cellular metabolism. As a consequence, exposing the respiratory system to exogenous pollutants will cause inflammation as well as irritation. Particle matter, in particular, has an impact on the human respiratory system. The effects of PS MPs (4.06 0.44 m) on human lung epithelial cells (BEAS-2B) at quantities ranging from 1 to 1000 g/cm^2 were examined. The findings from the studies demonstrated that PS MPs lead to cytotoxicity, increased lipid peroxidation, and an inflammatory response. Furthermore, the size distribution and density of PS MPs were found to alter the incidence of mitochondrial dysfunction [87]. Human pulmonary epithelial cells exposed to exceptionally high levels of PS nanoparticles demonstrated lethality and endoplasmic reticulum fatigue biological alterations [56]. In macrophages and pulmonary mucosal cell lines, PS with a length of 60 m caused ROS and ER stress, culminating in apoptosis of autophagic cells [88]. It was found that human pulmonary epithelial cells (Calu-3) and neutrophils (THP-1 cell lines) to PS nanobeads (50 nm) in order to cause DNA restitution and harmful and mutagenic and carcinogenic consequences on Calu-3 respiratory epithelium and THP-1 macrophages [89]. Furthermore, human alveolar type II epithelial cell cultures treated to PS nanoparticles (25 and 70 nm) demonstrated an effect on the amplification of NS-kB and proinflammatory cytokine microfiche, as well as a link among cell cycle and protein levels. As reported by various researchers, inhaling PS-MPs can lead to cancer [90]. Exposure concentration, dimension and duration, among other things, influence the potential hazardous effects of PS-NPs on pulmonary epithelial cells [91]. PS-MPs cause respiratory damage and worsen breathing problems. Furthermore, adult hepatocellular adenocarcinoma cells (A549) study the consequences of PS (amino-functionalized 100 nm) on under-fluid applied load when particulate absorption is increased [92]. Today, study on rats subjected to PS-MPs induced the creation of the proinflammatory proteins (TGF-) and TNF- elevated in lung parenchyma for 14 days, indicating that the impact is larger at the molecular scale than at the biological level [56].

5.3. Neuroendocrine System

There is significant proof that perinatal (prenatal and neonatal) exposures to EDCs (Endocrine Disrupting Compounds) found in microplastics, such as BPA and phthalates, cause central nervous system damage (CNS). They are caused by molecular and cellular alterations in the CNS, which can result in psychosocial, cognitive, learning, and neuropathological problems. It has been well established that BPA is vulnerable throughout the initial phases of life, like the infant and antepartum periods, and produces changes in the neurodevelopment [93]. On the other hand, there is certain scientific data that prenatal and neonatal BPA sensitivity is related to consternation [94] and morbidly depressed behaviors [95]. Remarkably, these results differ by gender, as females were more likely to acquire anxiousness than subjected males and female samples, whilst males displayed greater depressive--

like behaviors. These consequences are most likely an incidental result of poor GR and MR expression, which disrupts the GR-mediated regulation of the hypothalamic-pituitary-adrenal (HPA) circuit [96]. Research has investigated the impact of neonatal and perinatal BPA exposure on the human CNS. Ejaredar and colleagues conducted a comprehensive analysis a few years ago in which they investigated the connections among prenatal BPA susceptibility and behavior in children up to the age of 12 [97]. According to the researchers, the evaluated research shows that antepartum vulnerability to parental BPA is linked to nervousness, sadness, aggressiveness, and restlessness in children [97]. Presumably, if the vulnerability persists during adolescence, this might result in the occurrence of autism spectrum disorder (ASD) because studies have encountered those children with ASD had elevated serum and renal levels of BPA and related analogues contrasted with age-matched healthy volunteers [98]. The relationship involving prenatal phthalate toxicity and juvenile sensory perception and neurobehavior has piqued the research group's curiosity. Some researchers have done a comprehensive investigation to assess the status of information surrounding this correlation up to 2018 [99]. The researchers suggested that 26 documents (those that met their inclusion criteria) were reviewed, and that while the findings demonstrate a few discrepancies (gender- consequences, opposite repercussions, no statistical variabilities), they summarized that gestational sensitivity to DEHP, DBP, and BBP is connected with intellectual functioning, neurocognitive, and psychosocial functional limitations in children. Boys are more inclined than girls to have psychotic symptoms. While there are certain differences in the research on the relationship among perinatal phthalate exposure and CNS consequences, the majority of findings (preclinical and epidemiological) affirm that these universal EDCs cause progressive brain and cognitive difficulties that manifest in early life or adolescence in a sex-dependent manner.

5.4. Reproductive Alterations

Numerous investigations in transgenic mice show that EDCs can have an influence on the growth of both male and female reproductive systems at dosages comparable to predicted human subjection [100]. BPA, in specific, has been demonstrated to have the same effectiveness as E2 [101], and that in the presence of low epigenetic oestrogen levels, it may operate as an anti-estrogenic molecule, disrupting E2 function [102]. Additionally, moderate BPA subjection during pregnancy or the postnatal period is linked to a broad spectrum of endocrine-related diseases. Reproductive changes in females are strongly linked to follicular epigenetic modifications. These circumstances are most likely susceptible to BPA consequences during the epigenetic reconditioning of female progenitor cells, the formation of the mother's hybridization configurations, the preliminary distinctions and continuous adaptation of primordial follicle visceral constituents to the different phases of follicular growth, and luteal phase activity [103]. BPA exposure during pregnancy was linked to higher blood testosterone and oestradiol levels, lower progesterone levels in adulthood, and changed *in vitro* GnRH production. BPA exposure throughout these important developmental phases has been found to be damaging in terms of sperm quantity, shape, and function [104]. Furthermore, phthalates have a deleterious impact on male reproductive function in particular. A high rate of anterior prostate agenesis, a reduced occurrence of entire or partial ventral prostate agenesis, infrequent dorsolateral prostate and seminal vesicle agenesis, decreased sperm levels, and testicular, epididymal, and penile abnormalities were also observed as dose-related effects [105]. Only one epidemiological investigation in humans has found a link between maternal urine BPA levels at 12-16 gestational weeks and anus-genital distance (AGD, a measure linked to an increased peril of delayed libido, sterility, and testicular cancer in the progeny. A group found that children born to females with elevated BPA levels in their urine during gestation had a shortened AGD at 12 months than males born to mothers with insignificant BPA levels [106].

6. IS PREVENTION POSSIBLE

The topic of microplastic contamination was explored in recent prominent preliminary reports, with the conclusion that the ecological impact posed by such contamination is underestimated. Although certain views mentioned are controversial (for example, that *ex-situ* ecotoxicological investigations should look at microplastic-biota correlations at proportions equivalent to those seen in native habitat) and have a lot of validity. One generalization, though, pointed toward an additional concerning posture for toxicologists to take. Whilst microplastics are not customarily present at harmful levels in most ecosystems, trying to avoid microplastics from achieving such dangerous levels in the long term should not be deemed a poor guideline. Without question, prohibiting microbeads in the rinse-off cosmetic industry does not address contamination; but, a comprehensive strategy to prevent some ecological degradation before such loss is factually documented is required [107]. To that purpose, rational conceptions integrated with computational methods may be far more successful than conventional monitoring procedures at resolving microplastic threats to the environment. Methods for addressing microplastic contamination must emphasize source control, treatment, and cleansing. Concerning plastic (a significant source of residual MPs), significant efforts are being made to limit the marketization and use of single-use plastics, with an emphasis on plastic straws and carrier bags. Several nations have prohibited the utilization of single-use plastic packaging [108]. Engineering tools, bio - based or eco-friendly polymers, and biotechnological tools are the three types of remediation technologies, apart from traditional and global scale company – consumer regulations.

6.1. Engineering Tools

Waste water treatment plants (WWTPs) emit microliters and MPs into the ecosystem. Then, these facilities present a possibility to create and adopt unique MP contamination management solutions. Many studies investigated the potential of standard and new WWTP methods to eliminate microplas-

tics. Several results demonstrated that typical WWTP treatments remove a large fraction of the MPs in leachates (90-98%). Membranes, electrodeposition, and coagulation are the most often employed improvised treatment technologies [109]. Among the most effective is the membrane bioreactor (MBR), which combines a membrane technique such as microfiltration or ultrafiltration with biological effluent treatment. This approach outperformed the traditional activated sludge-based procedure in terms of MP extraction rate (99.4%). The efficacy of an MBR unit is that it terminates processing with microfiltration in eliminating MPs was also contrasted to that of WWTPs that used either supplementary (activated sludge) or contributory (granular sand filtration) intervention as an end of the process. The MBR system, which discharges 0.5 MPs L1, has the highest extraction efficiency (99.4%). MBRs were additionally contrasted to certain other emerging tertiary treatments, such as accelerated gravitational sand filters and dissolved air flotation, which remove MPs from both primary and secondary pollutants at rates greater than 95%. The bioactive filter (BAF) technology (which allows contaminant-degrading microorganisms to grow in it) also demonstrated excellent performance in removing MPs [110]. Moreover, the performance of electrocoagulation (EC), a well-known and proven technique for MP elimination from effluents, was investigated using simulated effluent containing varying proportions of PE microbeads. At diverse settings (starting pH, NaCl content, and current density), microbead removal percentage of >90% were reported, indicating that EC is an efficacious means of eliminating MPs from wastewaters. At a pH of 7.5, the best degradation efficiency of 99.24% was discovered [111]. Coagulation and ultrafiltration procedures have the promise to be used in drinking water treatment to remove MPs [112].

6.2. Use of Biobased and/or Biodegradable Polymers

Another approach to addressing the issue of the accumulation of polymers, MPs, and NPs is to employ additional biopolymer materials. Bioplastics are created from recyclable raw resources such as starches, cellulose, lignin, and bio - ethanol. Bioplastics at present account for around 0.5% of the roughly 335 million tonnes of plastic generated yearly, with this figure anticipated to rise to estimated 2.62 million tonnes by 2024 [113]. Bioplastics are categorized into three categories:

6.2.1. Biobased or Partially Biobased Non-biodegradable

like polytrimethylene terephthalate or thermoplastic polyester elastomers are examples. These materials are derived from biological origins but are as long-lasting as those derived from petroleum

6.2.2. Simultaneously Biobased and Biodegradable

Polylactic acid, polyhydroxyalkanoates, and polybutylene succinate are a few examples. They contribute to the serious issue of environmental degradation.

6.2.3. Based on Fossil Resources and Biodegradable

Polybutylene adipate terephthalate and polycaprolactone diol are two examples. They also help to alleviate the pollution issue but not the reliance of natural fuels.

Nonetheless, one investigation on the chemical alterations in the exterior of industrial PCLD (average molecular weight of 1250 Da) maintained under aerobic and denitrifying environments revealed solubilization in the sample after 7 days, providing hope for MP removal in WWTPs [114]. Certain recyclable and degradable bioplastics can be reduced by microbes producing nutrient-rich feedstock within as little as 3 months and without any pollutants or waste remaining. Compostable is currently chosen over biodegradable since it can be established according to information by European Bioplastics (2023) [115].

6.3. Bio-engineering Based Solutions

A further bioengineering-based alternative is to investigate novel biodegradation methods for traditional plastics, such as other varieties of microbes and fungus, or to extract the relevant biomolecules to achieve plastic solubilization. Extracellular carboxylesterases can digest biodegradable composites. Polymers can be destroyed by specific bacteria, such as Ideonella sakaiensis, and PE by the aquatic fungal species of Zalerion maritimum. Notwithstanding viable options, macro and micro plastics cleanup are still in its early stages at the bench scale. It is critical to find techniques for *in situ* MP degradation process by microbe inoculation or increased natural dissipation *via* local microbiota [116].

6.4. Corporate – consumer Responsibilities

According to research findings, reducing plastics and micro - plastic contamination is a growing societal duty. According to the findings of continuing research, the responsibilities of firms and customers, as well as their conduct (as people or companies), are critical in understanding why micro - plastics management is faltering at present. Many assessments have focused on personal consumer behaviour and top-down control, that is, regulations that prohibit people from utilizing plastic products and micro - plastics [117, 118]. It was asserted that reusing strategies to reduce microplastics requires community graces and pro-environmental attitude [117]. The incorporation of circular economy as the primary emergent answer shifts the focus mildly. Unless a circular economy is objective, consumers must explore the psychosocial viewpoints of enterprises, legislators, and funding agencies on microplastics in order to engage all sectors in the mutual objective of combating this developing threat to the world. Human responsible behaviour is always required because individual activities such as wasting, depositing, and poor reprocessing play a major role in the tremendous levels of plastic pollution. Plastic seems to be, however, used by people apart from average consumers. There are several industrial applications for plastic, and each business has its own drivers, such as the oil sector, which generates its feedstock. Studying the firm's perspective as a manufacturer and user of plastics remains a significant gap in re-

search [119].

CONCLUSION

The aggregation of microplastics in the atmosphere stresses ecosystems. We examined the most contemporary trends on the presence of microplastics in the surroundings and foodstuff, the eventual pathway of subjection in humans, and potential impacts in this overview. MPs are undeniably occurred in our meals, according to scientific research. As a technique to identify MPs, there are certain limits in the identification of particulates in such a measurable range provided, and their prevalence and abundance may be undervalued. Since practically all of the plastics ever manufactured continue to exist in the environment and worsens, it is inevitable that the food that is contaminated with MPs will grow over the coming years, if not decades. There are numerous potential negative health impacts induced by MPs or their hazards. A majority of investigations have been carried out to investigate the pollution of aquatic commodities, potable water (raw, treated, and kept in various containers), salt for personal food, and nectar, sugars, fruits, vegetables, and appropriate snacks. All of the aforementioned investigations pointed to a significant intake of microplastics through dietary intake. Many negative impacts of consumed microplastics, primarily PS, have been detected at elevated microplastic amounts when juxtaposed with human contact, indicating a danger to human well-being. More research must be undertaken to establish the real impacts of microplastic pollution at levels that fall within the spectrum of occupational exposure.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

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Valorisation of agro-industrial wastes: Circular bioeconomy and biorefinery process – A sustainable symphony

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ABSTRACT

In the quest for a sustainable future, the bio-economy and biorefineries have emerged as pivotal agents of transformation. This review paper offers an accessible and comprehensive exploration of the multifaceted bio-economy landscape. Environmental concerns, resource scarcity, and the demand for renewable and bio-based products are the key drivers shaping this sustainable paradigm. Agriculture and agro-industry play an indispensable role, acting as the primary suppliers of the essential feedstock for biorefineries. They not only fuel the bio-economy but also foster sustainable farming practices and rural development, forming a mutually beneficial relationship. Biorefineries, the workhorses of the bio-economy, optimize resource usage, minimize waste, and produce a diverse range of bio-based products. Innovative biorefinery techniques are at the forefront, revolutionizing efficiency and expanding the array of feedstock's, thereby creating higher value-added derivatives. These value-added products, spanning biofuels, bio-plastics, and more, drive the market towards a greener and circular economy. The bio-economy's commitment to sustainability is evident through waste reduction and the promotion of circular economy principles. Policy, regulation, and market developments shape the bio-economy by promoting bio-based industries while favouring eco-friendly alternatives, creating a competitive and healthy ecosystem. While the bio-economy shows promise, it faces challenges. Optimizing conversion efficiency, discovering new feedstocks, and solving biorefinery environmental issues need technological breakthroughs and research. In summary, the bio-economy and biorefineries orchestrate a sustainable symphony, driven by environmental consciousness, rooted in agriculture, refined by innovative techniques, and harmonized by the production of bio-based products. The stage is set for a greener, more sustainable future.

Bio-economy and biorefineries have become crucial drivers of transformation in the pursuit of a sustainable future. The review paper provides a thorough and easily understandable examination of the diverse bio-economy landscape. Environmental concerns, limited resources, and the need for biodegradable and renewable products are some of the main things that are shaping the sustainable paradigm. Agriculture and the agro-industry play a big role in this because they provide biorefineries with the feedstock they need. The bio-economy is not only fuelled by them, but they also contribute to sustainable farming practices and rural development, creating a mutually beneficial relationship. Biorefineries are the backbone of the bio-economy as they effectively utilize

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resources, minimize waste, and generate a wide array of bio-based products. At the forefront of innovation, biorefinery techniques are revolutionizing efficiency and expanding the range of feedstock's available. This, in turn, leads to the creation of higher-value derivatives and value-added products, such as biofuels and bioplastics, promoting a greener and more circular economy. The commitment of the bio-economy to sustainability is demonstrated through its efforts to reduce waste and promote the principles of a circular economy. Policy, regulation, and market developments impact the bio-economy by working together to support bio-based industries and encourage the use of eco-friendly alternatives. As a result, a competitive and healthy ecosystem is created. Although the bio-economy holds promise, it also encounters various challenges. Technological breakthroughs and research are necessary for optimizing conversion efficiency, discovering new feedstock's, and solving biorefinery environmental issues. In essence, a commitment to the environment guides how the bio-economy and biorefineries collaborate in a sustainable manner by utilizing innovative methods to refine and produce bio-based products. This harmonious process creates a symphony of sustainability, paving the way for the dream of a greener, more sustainable future.

1. Introduction

In the relentless pursuit of sustainable solutions to the global challenges of resource scarcity, environmental degradation, and climate change, the concept of the bio-economy has emerged as a beacon of promise (Gawel et al., 2019). In the tapestry of modern agriculture and agro-industry, encompassing the domains of agriculture, forestry, fisheries, and biotechnology, the bio-economy is an intricate thread that weaves together innovation, conservation, and economic growth (Kircher, 2021). It is a concept that not only defines a novel economic paradigm but also encapsulates the essence of human ingenuity in harmonizing with the natural world. The Duan, bio-economy, as a multifaceted construct, defies a single definition (Bauer et al., 2018). However, at its core, it represents a transformative shift from a traditional fossil fuel-based economy to one that hinges upon the sustainable utilization of biological resources and processes (Donner and de Vries, 2021). In the context of agriculture, it involves the judicious management of crops and livestock, harnessing genetic advancements, precision farming techniques, and eco-friendly practices to maximize productivity while minimizing environmental impact (Solis et al., 2020). Waste management is s significant problem in the agro based industrial sector which are accountable for air pollution, waste water contamination along with negative impact on the public health. The biological conversion of plant products has received more attention at present. Manufacturing of biofuels from the organic waste is a viable solution to the waste water treatment crisis (Naik et al., 2019). In forestry, it invokes the responsible stewardship of forests, recognizing them not merely as sources of timber but as reservoirs of biodiversity, carbon sequestration, and renewable energy. In fisheries, it emphasizes the sustainable harvesting of aquatic resources to safeguard both marine ecosystems and livelihoods. In biotechnology, it encompasses the relentless exploration of bio-prospecting, genetic engineering, and bioinformatics to create innovative products, fuels, and medicines derived from living organisms (Kircher, 2021). To appreciate the bio-economy's significance in our modern world, we must delve into its historical evolution, tracing its roots from the dawn of agriculture to the present-day confluence of science, industry, and environmentalism (Gawel et al., 2019). This journey reveals how societies have progressively recognized the finite nature of fossil fuels, the fragility of ecosystems, and the imperative of sustainable living. It underscores the bio-economy's evolution from a passive reliance on nature's bounty to an active commitment to shaping it for the betterment of humanity. Moreover, the urgency of transitioning from a fossil fuel-based economy to a bio-based one looms large on the horizon. Fossil fuels, once the lifeblood of industrial progress, now cast a shadow of peril over our planet (Solis et al., 2020). Climate change, air pollution, and resource depletion are the harbingers of a reckoning that compels us to shift our allegiance to bio-based alternatives. The bio-economy offers a lifeline-an opportunity to recalibrate our relationship with the environment, reduce greenhouse gas emissions, and foster economic growth through the sustainable utilization of biological resources (Gawel et al., 2019). However, issues arise due to the emission of hazardous byproducts from agricultural and industrial practices, such as pesticides, herbicides, and chemical fertilizers, into the environment. When these substances are discarded, they have the potential to leach into the soil and water, resulting in detrimental effects on ecosystems (Mosa et al., 2016). This can impact the well-being of plants, animals, and even human health if these contaminants penetrate the food chain. Further worry pertains to the presence of organic matter in these waste materials. Although organic matter might be advantageous in certain situations, an excessive accumulation of it from agro-industrial waste can give rise to complications. Eutrophication occurs when the decomposition of organic materials depletes the oxygen levels in water bodies. This process results in the reduction of oxygen levels, leading to the asphyxiation of aquatic organisms and causing disturbances in the equilibrium of ecosystems (Freitas et al., 2021). Furthermore, the inappropriate disposal of agro-industrial waste can lead to the deterioration of soil quality. These waste materials may contain substances that can alter the pH balance of the soil or introduce harmful ions. Over a period of time, this process can make the soil incapable of supporting plant growth, which in turn has a negative impact on agricultural output and the variety of living organisms in the area. Moreover, the substantial amount of agro-industrial waste produced poses significant difficulties, like the accumulation of toxic degradation products and the multiplication of pathogenic bacteria and fungi (Sadhukhan et al., 2016). Improper handling or disposal practices, such as open burning, can emit greenhouse gases into the environment, hence exacerbating global warming and climate change. Adopting sustainable waste management strategies is essential for mitigating these environmental challenges (Al et al., 2023).

This review paper systematically discusses the drivers of the bio-economy, emphasizing the role of agriculture and agro-industry within this paradigm. It explores biorefinery concepts and principles, particularly focusing on innovative biorefinery techniques. The paper investigates the production of bio-based products and value-added derivatives and scrutinizes sustainability considerations, emphasizing waste reduction and circular economy practices. Additionally, it delves into policy, regulation, and market trends, while also addressing the technological challenges and research frontiers associated with the bio-economy. This comprehensive analysis endeavours to provide a scientific understanding of the bio-economy, its potential for reshaping industries, and its vision of sustainability and innovation.

2. Factors influencing the growth and development of the bio-economy

The bio-economy, a transformative economic paradigm, is shaped by a complex interplay of factors that drive its growth and development. This scientific elaboration provides a comprehensive examination of these drivers, encompassing environmental concerns, resource scarcity, and technological advancements. Additionally, it underscores the indispensable role of policy, regulation, and international agreements in moulding the landscape of the bio-economy, illustrated through relevant

case studies (Gawel et al., 2019).

2.1. Environmental concerns and sustainability

Environmental concerns, notably the threat of climate change and the depletion of natural resources, have intensified the focus on sustainability in recent years. The bio-economy has gained prominence as it aligns with sustainability goals. It involves the use of renewable biological resources to produce various goods and services. For instance, biofuels derived from biomass can significantly reduce carbon emissions and contribute to mitigating climate change. These environmentally friendly alternatives are pivotal in addressing the pressing issue of global warming. Moreover, the bio-economy emphasizes a circular economy approach, where resources are used efficiently, waste is minimized, and materials are recycled. This circular economy model ensures a sustainable and responsible utilization of resources, making it a key driver of bio-economic growth (Goni et al., 2015).

2.2. Resource scarcity and circular economy

Resource scarcity, particularly concerning non-renewable resources like fossil fuels, has necessitated a shift towards a circular economy. In this context, biorefinery processes have gained importance. Biorefineries convert biomass into various valuable products, such as biofuels, bio-based chemicals, and materials. This approach minimizes waste and promotes the efficient use of resources, thus aligning with the principles of a circular economy. Biorefineries are central to the bio-economic model, as they contribute to resource efficiency by extracting the maximum value from biomass feedstock's while minimizing environmental impact (Maina et al., 2017).

2.3. Advancements in biorefinery technologies

Technological advancements have significantly impacted the bio-economy. These innovations enhance the efficiency and sustainability of biorefinery processes. One such advancement is enzymatic hydrolysis, a process that involves the use of enzymes to break down complex biomass into simpler, more valuable compounds. This method is more environmentally friendly and economically viable compared to traditional processes. It accelerates the conversion of biomass into bio-based products, furthering the growth and development of the bio-economy (Gawel et al., 2019).

2.4. Policy and regulatory support

Governments globally have recognized the potential of the bio-economy and have implemented supportive policies and regulations. These policies create a conducive environment for the growth of bio-based industries. They often include incentives, financial support, and guidelines for research and development in the bio-economic sector. Government support provides stability and assurance for businesses, fostering an ecosystem that encourages innovation and investment in bio-based technologies(Donner and de Vries, 2021).

2.5. Market trends and consumer demand

Recent market trends reveal a shift in consumer preferences towards more sustainable and eco-friendly products. There is an increasing demand for bio-based goods in various sectors, such as food, cosmetics, packaging, and construction materials. Consumers are more conscious of the environmental impact of their choices and are actively seeking products that align with their values. This shift in demand encourages businesses to invest in bio-based solutions, driving the growth of the bio-economy (Ronzon et al., 2020).

2.6. Technological challenges and research frontiers

Despite the progress made in biorefinery technologies, significant challenges persist. Research frontiers include the development of advanced biomass feedstocks, optimization of biorefinery economics to reduce costs, and the expansion of the range of bio-based products. Advanced feedstocks, such as algae and waste streams, are being explored to enhance the sustainability of biorefinery processes. Additionally, cost-effective production methods are under investigation to make bio-based products more competitive in the market. Expanding the variety of bio-based products further maximizes the potential of the bio-economy by catering to diverse industrial needs (Awasthi et al., 2019).

3. Factors and related case studies

3.1. Environmental concerns

One of the primary catalysts behind the bio-economy is the mounting concern for the environment. As global climate change escalates, biodiversity dwindles, and pollution proliferates, the imperative for a sustainable alternative to the traditional fossil fuel-dependent economy becomes increasingly evident (Solis et al., 2020). The bio-economy offers a compelling solution by prioritizing practices that are in harmony with the natural world. The bio-economy strives to reduce greenhouse gas emissions through the use of renewable resources and processes. Sustainable agriculture practices, including organic farming and precision farming (Duan et al., 2020) not only increase crop yields but also mitigate the environmental footprint of food production (Sillanpää and Ncibi, 2017). Moreover, circularity in resource utilization, a core principle of the bio-economy, ensures that waste from one process becomes a valuable input for another, minimizing environmental degradation (Maina et al., 2017). *Case study 1: Sweden's sustainable forestry*: Sweden, renowned for its commitment to sustainability, exemplifies the bio--economy's environmental ethos. The country practices sustainable forestry, maintaining a delicate balance between timber production and ecological conservation. Sweden's forest management ensures the preservation of biodiversity, carbon sequestration, and the production of bio-based materials, contributing to the country's robust bio-economy.

3.2. Resource scarcity

Resource scarcity, particularly in the context of finite fossil fuels and non-renewable raw materials, has emerged as a formidable challenge. The bio-economy, however, presents a paradigm shift towards resource abundance within the biological realm. By harnessing biologically derived materials, biofuels, and bioproducts, the bio-economy addresses resource scarcity while simultaneously unlocking the potential of renewable resources. Biofuels, such as biodiesel and bioethanol, exemplify this approach (Tsegaye et al., 2021). These biofuels offer renewable alternatives to their fossil fuel counterparts, mitigating the strain on finite fossil fuel reserves while reducing greenhouse gas emissions (Solis et al., 2020). Additionally, sustainable forestry practices, such as selective timber harvesting and reforestation, ensure a perpetual source of renewable wood products, all while safeguarding biodiversity and acting as carbon sinks. *Case study 2: Brazil's Ethanol Industry*: Brazil's bio-economy success story lies in its ethanol industry. The country produces bioethanol from sugarcane, providing a renewable alternative to gasoline. Brazil's commitment to sustainable sugarcane cultivation and bioethanol production not only reduces reliance on fossil fuels but also stimulates economic growth and job creation, making it a pivotal driver of the bio-economy.

3.3. Technological advancements

The relentless pace of technological advancements has been

instrumental in propelling the bio-economy forward. Innovations in biotechnology, nanotechnology, and data analytics have revolutionized the way biological resources are harnessed and processed (Awasthi et al., 2019). These advancements have significantly enhanced productivity and resource efficiency within the bio-economy. Precision agriculture, empowered by sensor technology and data-driven insights, maximizes crop yields while minimizing resource use. Gene editing techniques, such as CRISPR-Cas9, enable the development of tailored crops with improved yields and resistance to pests and diseases. Furthermore, bioprocess optimization ensures efficient conversion of biological feedstock's into valuable products, reducing waste and resource consumption (Bastos Lima, 2018). *Case study 3: Precision agriculture in the United States:* The United States has harnessed technological advancements to optimize agriculture. Precision agriculture utilizes sensors, GPS technology, and data analytics to tailor farming practices to individual field conditions. By minimizing resource waste and maximizing yields, precision agriculture serves as a testament to how technology drives the bio-economy.

3.4. Role of policy, regulation, and international agreements

3.4.1. National policies and regulations

The bio-economy's growth and development are intricately linked to national policies and regulations. Governments play a pivotal role in fostering an environment conducive to bio-economic progress. Policy initiatives often include incentives for renewable energy adoption, subsidies for sustainable agriculture, and funding for research and development in biotechnology (Gawel et al., 2019). For instance, the United States' Renewable Fuel Standard (RFS) mandates the incorporation of renewable biofuels into the nation's fuel supply, stimulating the growth of the biofuel industry (Tsegaye et al., 2021). Likewise, the European Union's Common Agricultural Policy (CAP) promotes sustainable farming practices, aligning with the principles of the bio-economy (Ronzon et al., 2020). *Case study 4: Germany's bio-economy policy:* Germany's bio-economy policy strategy outlines a comprehensive approach to advancing the bio-economy. The strategy encourages innovation, sustainable resource management, and cross-sectoral collaboration. Through dedicated funding and policy incentives, Germany is shaping its bio-economy landscape and promoting sustainable growth (Donner and de Vries, 2021).

3.4.2. International agreements

International agreements provide a critical framework for global cooperation in the bio-economy (Donner and de Vries, 2021). The Paris Agreement, a landmark international accord, compels nations to reduce carbon emissions and transition to renewable energy sources, in alignment with bio-economy objectives. Similarly, the Convention on Biological Diversity seeks to ensure the equitable and sustainable use of biological resources, reinforcing the bio-economy's commitment to responsible resource management(Donner and de Vries, 2021). Moreover, international trade agreements play a vital role in shaping the global bio-economy. Agreements facilitating the cross-border exchange of bio-based products can expand markets and incentivize innovation (Ronzon et al., 2020). *Case Study 5: The European Union's Circular Economy Package:* The European Union's Circular Economy Package aligns with bio-economy principles by emphasizing resource efficiency and sustainability (Maina et al., 2017). The package promotes the use of renewable and bio-based materials, fosters food waste recycling and reuse, and reduces waste. This comprehensive approach exemplifies how international agreements can harmonize with the bio-economy to drive global sustainability (Ronzon et al., 2020).

3.4.3. Harmonization of regulations

The harmonization of regulations across countries and regions is imperative for fostering a level playing field for bio-based industries. Collaboration is necessary to establish common standards for sustainability, bio-security, and ethical considerations (Solarte-Toro and Cardona Alzate, 2021). The European Union's efforts to harmonize regulations for bio-based products and biotechnology exemplify this approach. By creating a consistent regulatory framework, the EU facilitates the growth of a vibrant bio-economy within its member states, fostering innovation and market expansion (Ronzon et al., 2020).

3.5. Role of agriculture and agro-industry in the bio-economy

Agriculture and agro-industry constitute the primary pillars of the bio-economy, serving as its bedrock foundation (Bauer et al., 2018). The concept of the bio-economy rests upon a foundation of biological resources, sustainable practices, Innovation, agriculture, and agro-industry are pivotal in shaping this transformative economic model (Donner and de Vries, 2021). Together, these elements contribute significantly to the growth and evolution of the bio-economy (Gawel et al., 2019). Biological Resources, including crops, livestock, forests, and aquatic ecosystems, are the lifeblood of the bio-economy. These biological assets provide the essential raw materials that fuel a diverse range of bio-based industries. Crops such as corn and sugarcane, along with forest biomass, serve as the primary feedstocks for biorefineries (Bastos Lima, 2018). Within these facilities, these biological resources are transformed into a multitude of valuable products, spanning from biofuels to bioplastics, bio-chemicals, and biomaterials (Tsegaye et al., 2021). Moreover, these resources also play a pivotal role in the generation of renewable energy sources, acting as sustainable alternatives to fossil fuels (Solis et al., 2020). The bio-economy capitalizes on the inherent regenerative capacity of these biological resources, perpetuating the cycle of sustainability. Sustainable Practices are at the heart of the bio-economy's commitment to environmental and economic sustainability (Solarte-Toro and Cardona Alzate, 2021). In agriculture and agro-industry, responsible land use practices ensure that the activities do not harm ecosystems or degrade soil quality. Practices like agro-forestry, organic farming (Duan et al., 2020), and eco-system friendly agricultural methods prioritize biodiversity conservation. They create a harmonious coexistence between agricultural endeavors and the preservation of natural habitats. Furthermore, sustainability in these sectors extends to resource efficiency, with a focus on judicious water use, reduced reliance on fertilizers, and responsible pesticide management (Sillanpää and Ncibi, 2017). These practices not only reduce environmental impact but also enhance resource efficiency, contributing to the bio-economy's core principles. Innovation is the dynamic force propelling the bio-economy forward. Agricultural and agro-industrial sectors serve as dynamic hubs for technological advancements. Biotechnology innovations such as genetic engineering and gene editing have led to the development of high-yield, disease-resistant crops (Kircher, 2021). These innovations increase crop productivity while reducing the need for chemical inputs, aligning seamlessly with sustainable practices. Precision agriculture, another outcome of innovation, leverages technology, data analytics, and sensor-driven insights to optimize farming practices. This optimization results in efficient resource utilization, increased crop yields, and decreased environmental impact. Innovation also extends to the creation of value-added bioproducts, including bioplastics, bio-based chemicals, and novel food products (Sillanpää and Ncibi, 2017). Agricultural feedstocks (Konwar et al., 2018)are the linchpin of this transformation, representing nature's renewable capital. These feedstocks encompass a wide spectrum of plant-derived resources, including, but not limited to, crops such as corn, sugarcane (Bastos Lima, 2018), soybeans, and wheat. Each of these agricultural feedstocks plays a pivotal role in shaping the bio-revolution. Research and development in agro-industry lead to breakthroughs in processing and extraction methods, enhancing the economic viability of these products. Furthermore, innovation drives solutions in the realm of circular economy by finding novel ways to repurpose agricultural residues and waste, ultimately reducing overall waste generation (Maina et al., 2017). This triumvirate not only propels economic growth but also serves as a

powerful engine for environmental sustainability (Solarte-Toro and Cardona Alzate, 2021). The bio-economy stands as a transformative model, fostering a harmonious relationship between economic prosperity and ecological well-being, ushering in a more sustainable and regenerative future (Donner and de Vries, 2021).

4. Challenges and opportunities in integrating bio-economy principles in agro-industry sectors

Integrating bio-economy principles into agro-industry sectors comes with its share of challenges (Gawel et al., 2019). Resource competition, for instance, involves the complex task of balancing the use of limited land and essential resources between food production and bio-based feedstock cultivation. Sustainable practices are required to prevent the overexploitation of resources and degradation of the environment (Solarte-Toro and Cardona Alzate, 2021). High initial investments for infrastructure and research present financial barriers to the transition. However, these challenges are met with significant opportunities. Sustainable land management practices and resource-efficient approaches offer solutions to resource competition. Adoption of sustainable agriculture, agro-forestry, and responsible resource use promote environmental conservation. Attracting investments, both private and public, can drive growth in bio-based industries, and supportive policy frameworks can facilitate this (Gawel et al., 2019). The adoption of circular economy practices enhances resource utilization and reduces waste, while the expansion of the bio-economy creates job opportunities, particularly in rural areas (Maina et al., 2017). Some opportunities and challenges in integrating bioeconomy principles in agro-industry sectors are shown in Table 1. Finally, encouraging research and development fosters innovation, leading to technological advancements that benefit both sectors and contribute to the overall success of the bio-economy integration (Solarte-Toro and Cardona Alzate, 2021).

Table 1
Challenges and opportunities in integrating bioeconomy principles in agriculture and agro-industry sectors.

Aspect	Challenges	Opportunities	References
Resource competition	Balancing food production with bio-based feedstock production on limited land Competition for resources (e.g., water, fertilizers)	Sustainable land management for dual-purpose crops Innovative resource-efficient practices	(Sillanpää and Ncibi, 2017)
Sustainability	Ensuring sustainability of agricultural practices Avoiding overexploitation of resources	Adoption of sustainable agriculture and agroforestry Promotion of responsible resource use	(Sillanpää and Ncibi, 2017; Solarte-Toro and Cardona Alzate, 2021)
Infrastructure and investment	High initial investments required for biorefinery infrastructure and research	Attracting private and public investments in bio-based industries Developing supportive policy frameworks	(Gawel et al., 2019)
Circular economy	Insufficient utilization of agricultural residues and waste	Promoting circular economy practices through efficient waste utilization	(Maina et al., 2017)
Job creation	Ensuring equitable job distribution in rural areas	Job creation in rural areas through sustainable agriculture and bio-based industries	(Ronzon et al., 2020)
Innovation	Limited R&D in sustainable agriculture and bio-based industries	Encouraging research and development to drive technological advancements	(Bauer et al., 2018)

5. Biorefinery as a concept

The concept of biorefinery represents (Fig. 1) a pioneering approach in resource utilization, aligning closely with the principles of sustainability and environmental responsibility (Sillanpää and Ncibi, 2017). Biorefineries are dynamic facilities that transform various forms of biomass, such as agricultural residues, forestry by-products, and algae, into a spectrum of valuable products, including biofuels, bioplastics, bio-chemicals, and biomaterials (Solarte-Toro and Cardona Alzate, 2021). Carbon sequestration, bioenergy generation, and the creation of bioproducts are all advantages of using biomass, which is recognised as a renewable carbon source (Bauer et al., 2018). The availability of biomass as a source of energy streams (fuel and energy) and the maximum conversion yields are also constraints. Seasonality, regional accessibility, and relatively low calorific value are obstacles to the effective utilisation of biomass as a renewable carbon source ("Biomass Gasification, Pyrolysis and Torrefaction: Practical Design and Theory - Prabir Basu - Google Books, 2018) (Sharma et al., 2020). The delicate issue of the cultivation of arable land for food production is addressed by the sustainable production of biomass (Gavrilescu, 2014). The integrated biorefinery is taken into consideration in order to maximise the utilisation of biomass, including the wastes created from the different conversion routes, and transform them into valuable bio-based product streams. According to (Cherubini, 2010) and (Ferreira, 2017), a biorefinery is a type of infrastructure where various conversion technologies, which comprises thermochemical, biochemical, combustion, and microorganism growth platforms, are integrated to effectively produce streams of sustainable bio-based products, including biofuel (Tsegaye et al., 2021), bio-chemicals, bioenergy, and other high-value bio--products. The idea of a biorefinery has recently been developed and is being used to process different biomass feedstock's such lignocelluloses (Konwar et al., 2018), algae (Solis et al., 2020) and other kinds of waste. A biorefinery is akin to a multifaceted industrial complex, akin to petroleum refineries, but harnesses biological feedstock's for the production of bio-based commodities. The essence of biorefinery lies in the efficient utilization of diverse biological resources, recognizing the intricate composition of biomass (Conteratto et al., 2021). Unlike traditional single-product processes, biorefineries adopt an integrated approach, extracting multiple products from the same feedstock. This versatility is the cornerstone of sustainable resource utilization within the bio-economy. At its core, the biorefinery concept revolves around the synergy of biochemical and thermochemical processes (Bauer et al., 2018). It combines technologies such as fermentation, pyrolysis, and chemical conversion to unlock the latent potential of biomass. By doing so, biorefineries mirror the efficiency and versatility of their petroleum-based counterparts while enhancing the sustainability quotient (Solarte-Toro and Cardona Alzate, 2021). They foster the principles of sustainability by reducing waste generation, diminishing greenhouse gas emissions, and promoting the circular economy (Maina et al., 2017).

6. Biorefinery types

Sustainable resource utilization is a pivotal theme in the modern world, primarily driven by concerns of resource scarcity and environmental degradation. Biorefineries are positioned at the forefront of addressing these challenges through their intrinsic relationship with sustainable resource utilization (Table 2).

6.1. *Lignocellulosic biorefinery*

Lignocellulosic biorefinery is a cutting-edge technology that

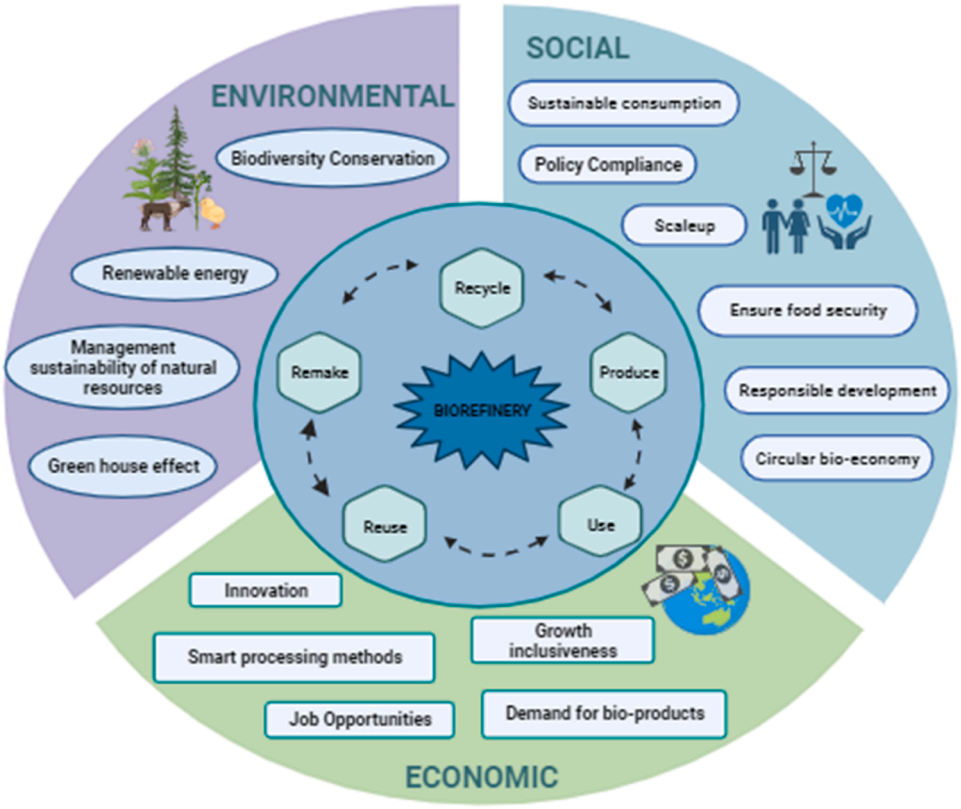

Fig. 1. Aspects of biorefinery-based approach.

Table 2
Conventional approach vs. biorefinery-based approach on various aspects of bio-economy.

Aspect	Conventional approach	Biorefinery-based approach	References
Resource utilization	Often linear processes with single-product outputs Limited use of biomass, resulting in waste and inefficiency	Integrated approach to maximize resource use Multiple valuable product streams from the same biomass source Efficient utilization of underutilized or waste fractions	(Gawel et al., 2019)
Waste generation	Generates significant waste, especially in byproduct or residue streams May require additional waste management	Reduces waste generation through multifunctional processes Converts waste into valuable products, promoting a circular economy	(Maina et al., 2017)
Resource efficiency	Resource use is often suboptimal, leading to inefficiency Focus on primary product output with limited diversification	Optimizes resource use, minimizing resource waste Diversifies biomass utilization, enhancing resource efficiency	(Gawel et al., 2019)
Circular economy principles	Linear processes lead to a lack of integration and closed-loop systems Limited waste repurposing or recycling	Exemplifies circular economy principles through multiple product extraction Efficiently converts waste into inputs, promoting sustainability	(Kircher, 2021)
Greenhouse gas emissions	May rely on fossil resources, contributing to carbon emissions Carbon-intensive processes may be common	Reduces reliance on fossil resources, mitigating greenhouse gas emissions Sustainable alternative to carbon-intensive industries	(Solis et al., 2020)
Resource conservation	Limited consideration for resource conservation or long-term sustainability Potential overexploitation of natural resources	Promotes resource conservation, emphasizing efficient use Addresses sustainability concerns, protecting natural resources	(Sillanpää and Ncibi, 2017)

capitalizes on the immense potential of lignocellulosic biomass, including agricultural by-products like wheat straw, maize stalks, and rice straw (Baruah et al., 2018). This sustainable approach uses lignocellulosic enzymes, primarily derived from fungi, to break down complex materials into valuable components. Key enzymes involved include cellulases for cellulose degradation, xylanases for hemicellulose deconstruction, and ligninases for modifying lignin. These enzymes are instrumental in transforming these biomass sources into not only bioenergy but also an array of high-value products, such as chemicals and biofuels (Baruah et al., 2018). Moreover, the repurposing of lignin components, traditionally seen as a hindrance in biofuel production, opens doors to various applications, from adhesives to plastics. In essence, lignocellulosic biorefinery embraces sustainable agricultural practices, mitigates climate change, and advances the transition to a bio-based circular economy. It represents a pivotal innovation in sustainable biomass utilization, with far-reaching environmental and economic benefits.

In contrary to first-generation biomass feedstock's, which compete with the need for land for food crops, lignocellulosic biomass is a second-generation biomass feedstock (Konwar et al., 2018). They are a useful source of biomass feedstock due to the variety of plants they may be used with and their widespread availability in tropical areas. Only 3 % of the 1.3 billion tonnes of lignocellulosic biomass produced each worldwide is used to make bio-chemicals, bioenergy, and items unrelated to food

(Baruah et al., 2018). Barley straw, coconut husks, maize stover, empty fruit bunches; rice, sugarcane bagasse, straw, sorghum stalks, wheat and wood are the main sources of lignocellulosic biomass (Konwar et al., 2018). It is made up of lignin, hemicelluloses, and cellulose, which may be processed into a variety of different products in a biorefinery by lignocellulosic fractionation (Zhang, 2008). Lignocellulosic biorefineries were suggested by (De Bhowmick et al., 2018) as a platform for addressing the sustainable development of high-valued bio-products alongside the production of biofuels. They emphasised that reusing biomass and its wastes, as well as integrating various conversion technologies via process integration, are viable options for the manufacture of bioproducts in a sustainable manner (Kircher, 2021).

6.2. Algal biorefinery

Algal biomass is recognised as an advanced (third-generation) biomass feedstock that offers advantages over lignocellulosic biomass, including reduced land requirements and increased biomass production and output (Solis et al., 2020). Macroalgae and microalgae biomass are the two primary subcategories of algal biomass (Chew et al., 2017; Torres et al., 2019). According to (Leu and Boussiba, 2014), microalgae are photosynthetic microorganisms that effectively use solar energy to accumulate biomass made up of vital biological components. In contrast to traditional methods of culture, microalgae may be cultivated in a variety of reactor systems, including vertically planned and constructed photobioreactors (Ubando et al., 2020). In order to create multiple microalgal-based products in a sustainable manner, a number of biorefinery methods, particularly for microalgae biomass, have been developed (Chew et al., 2017; López Barreiro et al., 2014). Seaweeds classified as macroalgae are marine microorganisms that are mostly cultivated offshore and are prevalent along coastal shorelines (Lehahn et al., 2016). In order to produce food and high-value goods like biofuels and bio-chemicals, they provide a sustainable supply of bio-compounds (Jiang et al., 2016). For the manufacture of highly valuable bio-products from seaweeds, the development of macroalgae-based biorefineries was presented (Ingle et al., 2018; Sadhukhan et al., 2016). The breakdown of hemicelluloses and cellulose from lignocellulosic biomass into bio-compounds required for fermentation is facilitated by microbes, which may exist as single cells or flourish in multicellular environments (Jin et al., 2015). The microbial biorefinery systems may produce biofuels by fermentation (Almeida et al., 2012; Jiang et al., 2017). From the standpoint of a biorefinery (Hasunuma et al., 2013) conducted a comprehensive assessment of several microorganisms utilised to produce biofuel from lignocellulosic biomass.

6.3. Waste biorefinery

The manufacture of bio-based goods including biopolymers, biofuels, and bio-chemicals utilising wastes (non-edible feedstock's, and biogenic wastes) has become a viable alternative (Venkata Mohan et al., 2014). Wastes are a crucial part of CBE, and there are potential for reuse, recycling, and remanufacturing since the majority of conversion technologies and channels are established and easily accessible. Waste characterisation (Skaggs et al., 2018) and the development of waste-to-energy facilities have been carried out in order to further allow an effective and successful conversion from waste to bioenergy. By using the biorefinery idea, it is possible to produce bioenergy from trash in a sustainable manner. Food waste, lignocellulosic waste, paper waste, municipal solid waste, and other waste types have all been the subject of biorefinery studies in the past (Barampouti et al., 2019; Bastidas-Oyanedel and Schmidt, 2018). Nizami et al. (2017) reviewed several waste biorefinery pathways in poor nations in the context of a circular economy. The waste biorefinery using the CBE framework provides a comprehensive approach to addressing numerous facets of environmental, social, and economic problems as the waste problem worsens (Minelgaitė and Environment, 2019).

7. Innovative biorefinery techniques

The quest for sustainable resource utilization and the transition towards a circular bioeconomy has prompted the development of innovative biorefinery techniques (Maina et al., 2017). These pioneering approaches capitalize on the inherent complexity of biomass, unlocking its full potential through enzymatic and microbial conversion processes, advanced separation and purification techniques, and the transformative power of biotechnology (Kircher, 2021). Here, we explore the dynamic landscape of innovative biorefinery techniques (Fig. 2), highlighting their profound impact on biomass deconstruction, valorisation, and the advancement of the bioeconomy (Conteratto et al., 2021).

7.1. Gasification

The gasification process refers to a thermochemical procedure wherein carbonaceous materials are transformed into syngas, which is a composite of hydrogen, carbon monoxide, carbon dioxide, methane, higher hydrocarbons, and nitrogenunder high temperatures ranging from 500 to 1400 °C, at pressures up to 33 bar, and with minimal or no presence of oxygen (Lee et al., 2019). The aforementioned procedure is the optimal approach for biomass-derived hydrogen gas production, as it aligns with the fundamental laws of energy balance. Gasification is a process that yields various important outputs, including biofuel, hydrogen gas, biomethane gas, heat, power, and chemicals (Lee et al., 2019). Biomass gasification demonstrates a higher ability for energy recovery and a larger heat capacity in comparison to combustion and pyrolysis methodologies. Oxidizing waste materials in the presence of oxidants, biomass gasification is commonly used as indirect combustion process to convert municipal solid waste into synthetic gases or fuel (Banu et al., 2020). The process of catalytic methanation involves the conversion of carbon monoxide and carbon dioxide, which are often found in syngas, into synthetic natural gas. This conversion process offers an added benefit to the overall gasification process. Biowaste gasification utilizes a range of gasifiers, such as fixed bed, fluidized bed, entrained flow, and plasma gasifiers (Lee et al., 2019). The gasification process results in the production of substantial quantities of carbon dioxide (CO_2) and carbon monoxide (CO) when utilizing feedstock that has elevated levels of carbon and oxygen. Bimetallic catalysts, including Nickel, Ruthenium, Copper, and Cobalt, have demonstrated the ability to augment the reforming process and expedite the generation of hydrogen and methane.Plasma gasification is a promising thermochemical technique that exhibits the ability to efficiently handle and process hazardous leftover biomass (Lee et al., 2019). The process is dependent on external energy sources in order to maintain higher temperatures, resulting in the production of syngas, slag, and ash. The utilization of plasma co-gasification has been employed as a means to extract energy from both municipal solid waste and solid plastic trash, resulting in a significant enhancement in the overall efficiency of the plant.

7.2. Pyrolysis

Pyrolysis is the thermal decomposition of biomass in an oxygen-free environment, often taking place within a temperature range of 350 to 550 °C, and occasionally reaching temperatures as high as 700 °C (Lee et al., 2019). Biochar is a carbon containing substance that is produced by applying high temperature to additional lignocellulosic material or thermal pyrolysis of agricultural waste (Kaur et al., 2023). The pyrolysis process entails the thermally induced breakdown of organic compounds, leading to the formation of a heterogeneous combination carbon dioxide (CO_2), methane (CH_4) hydrogen (H_2), Carbon monoxide (CO) are the gaseous materials along with production of a liquid and solid phase/char (Rodionova et al., 2022). A significant differentiation between gasification and pyrolysis pertains to the production of a fuel gas that may be efficiently utilized for combustion, hence enabling the generation of

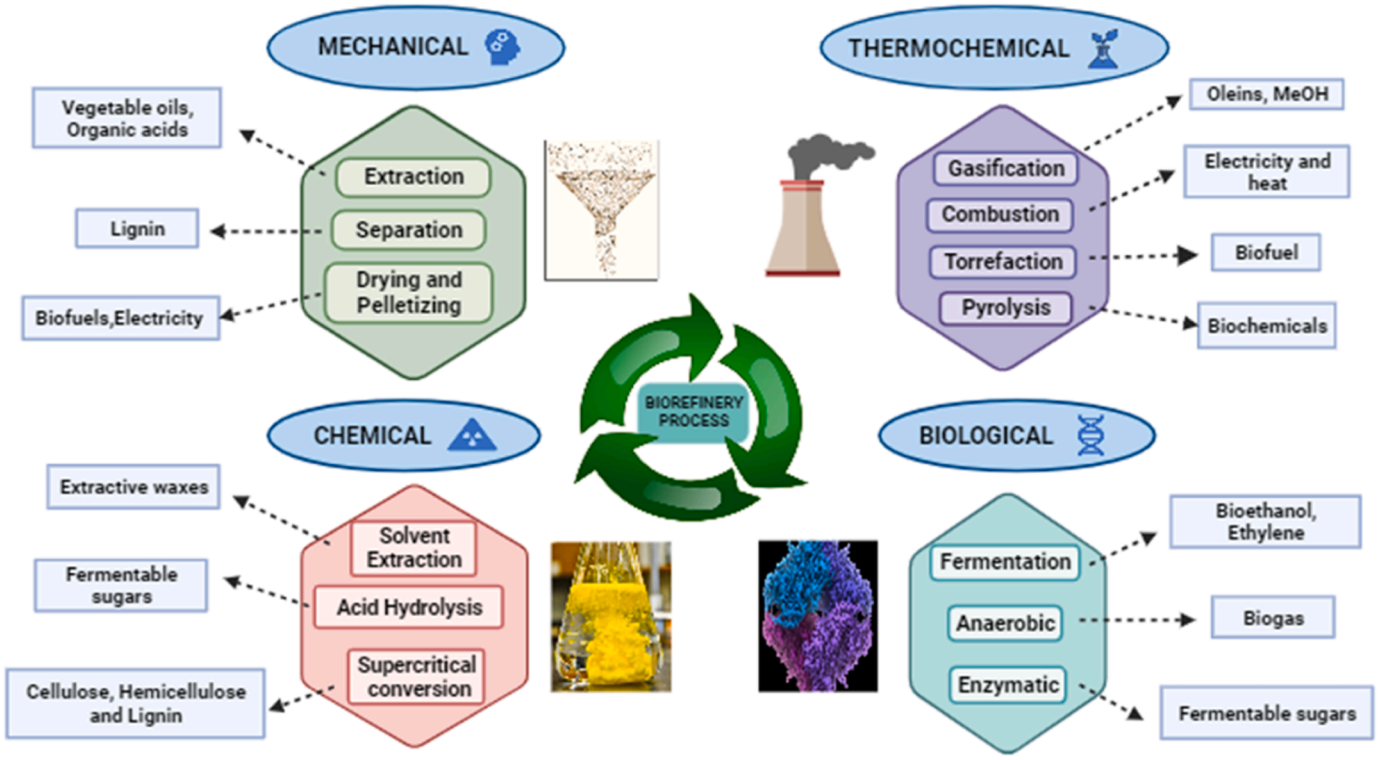

Fig. 2. Integrated biorefinery processes.

heat. The process of pyrolysis results in the production of a liquid fuel known as pyrolysis oil, often referred to as py-oil or bio-oil. This fuel has the potential to be used as a substitute for fuel oil in a range of applications, including static heating and power generation. One notable benefit of the liquid fuel produced via pyrolysis, as opposed to the fuel gas formed through the gasification process, lies in the convenience of storing and transporting the resulting bio-oil. There exist three unique pyrolysis processes that can be differentiated by their operational parameters: slow pyrolysis, quick pyrolysis, and flash pyrolysis (Lee et al., 2019). The formulation of their products is determined by the current operational circumstances. The phenomenon of slow pyrolysis involves the decomposition of organic matter, leading to the formation of char. Slow pyrolysis is conducted around temperatures ranging from 350 to 750° C with a heating rate around 10° C/min (Patel et al., 2016). The overall yield is around 35 % biochar, 35 % syngas and 30 % condensable materials. The composition varies depending on heating rate, temperature, and vapour residence time (Patra et al., 2021). A longer residence time enables primary products to undergo conversion giving rise to tar, coke, heat stabilized products and this pyrolysis is seldom referred as carbonization (Bi et al., 2022). The aforementioned procedure takes place under conditions of relatively low temperatures, characterized by a gradual increase in heat and a prolonged duration for the vapours to persist. The main outcome of fast pyrolysis is the generation of bio-oil. This is accomplished by subjecting the material to controlled temperatures of approximately 500 °C, a brief residence time of less than 2 s, and a high heating rate surpassing 200 $°C^{s-1}$. Flash pyrolysis is characterized by a notably short reaction period and a higher rate of heating in comparison to rapid pyrolysis (Lee et al., 2019). Currently, there is a heightened focus on the production of liquid goods using the fast pyrolysis method. The rationale behind this phenomenon may be ascribed to the advantages linked to the substantial production of py-oil, which can attain a weight percentage of up to 75 % (Lee et al., 2019). Additionally, the cost-effectiveness and energy efficiency of this method, together with its ecological benefits, further contribute to its appeal. Py-oil exhibits a dark brown hue and possesses a notable level of viscosity. The fuel in question employs a low calorific value and consists of several chemical components, including acids, alcohols, aldehydes, phenols, and oligomers, which are generated from lignin. In recent years, there has been a notable emphasis on improving the properties of py-oil (Lee et al., 2019) There is a necessity to enhance the quality of py-oil to enable its utilization as a viable substitute for crude oil. There are various approaches available for the upgrading of pyrolysis oil, which include physical, chemical, and catalytic methods.

7.3. *Anaerobic digestion*

Microalgae biomass contains carbohydrates, proteins, and lipids, which may improve economic, sustainability, and environmental aspects of biorefineries. Anaerobic digestion of biodiesel feedstock residual may optimize nutritional extraction. Anaerobic digestion converts microalgae material into biogas using bacteria. Biogas consists mostly of methane (CH_4), carbon dioxide (CO_2), and low levels of hydrogen sulphide. Biogas typically has 20–40 % of the biomass's lower heating value (Lee et al., 2019). Anaerobic digestion can handle 90 % moisture. The main steps are hydrolysis, fermentation, and methanogenesis. Hydrolysis breaks down biomass macromolecules into simpler ones. Fermentation then produces alcohols, acetic acid, fatty acids, and H_2 and CO_2 gasses from these simpler biomolecules. Methanogens processed the gas mixture to produce biogas with 60–70 % CH_4 and 30–40 % CO_2 (Lee et al., 2019). When in comparison to other technological processes, anaerobic digestion is highly recommended for promoting renewable energy as it produces energy carriers through reliable methods and does not require oxygen as well as permits the reuse of leftover biomass in agriculture (Choudhary et al., 2020). The microalgae biomass contains carbon, nitrogen, phosphorus, and trace elements like iron, zinc, and cobalt (Lee et al., 2019). These trace elements promote methanogenesis. Knowing the organic compounds in microalgae biomass allows estimates of CH_4 and NH_3 synthesis by anaerobic digestion. Despite their slower breakdown rate than carbs and proteins, lipids boost methane generation. Researchers observed that hydrolysis of bio compounds for

anaerobic digestion took 0.18, 0.43, and 3.2 days for carbohydrates, proteins, and lipids, respectively (Lee et al., 2019).

Biogas generation and energy content depend on biomass nutrient composition, operation temperature and pH, biomass loading rate, and hydraulic and solid retention length. Optimization of hydraulic and solid retention time is necessary to ensure that slow loading rates do not impair the rate-determining hydrolysis process and rapid loading rates do not limit methanogenesis. The difficulty of hydrolysing microalgae cell walls limits the hydrolysis process. Thus, microalgae species selection affects loading rates and retention time. The methanogenesis pH level is crucial to biogas CH_4 percentage improvement. Microbial colonies release NH_3, a nitrogen waste product, during fermentation, raising pH. Carbon dioxide (CO_2) solubilization in the fermentation medium promotes biogas methane (CH_4) buildup as pH rises. Methane (CH_4) concentration increases biogas energy, making it beneficial (Lee et al., 2019). In addition to pH, high operating temperatures boost microbial activity and CH_4 generation. Increasing the temperature from 15 to 52 °C with Spirulina maxima biomass boosted CH_4 productivity and volatile solids reduction by 35 % (Lee et al., 2019). Low biomass concentration in the feed stream is a major challenge for anaerobic digestion. A study found that anaerobic digesters work best with a microalgae biomass concentrating stage. The biomass feed stream was too diluted, destroying microbial populations due to insufficient digestible nutrients. Another issue is microalgae cell walls' resistance to hydrolysis. We can use cell disruption on microalgae biomass to break down cellular barriers. Microalgae cells hydrolyse nutrients, making them available to microbial populations.

7.4. Transesterification

The utilization of potential biomass, namely cellulosic biomass, in the production of biofuels presents a more intricate process due to the necessity of adjusting the qualities and performance of the extracted oil to align with the characteristics of hydrocarbon-based fuels (Lee et al., 2019). A variety of catalyst, including ionic liquids, acidic or alkaline catalyst, and carbon based catalyst are capable of speeding up the process. The populus method for production of biodiesel is through homogeneous alkaline catalysis. The capability to rapidly attain an enormous conversion yield and accelerate the reaction at low temperature and air pressure is the contributing factor for this approach (Tsavatopoulou et al., 2021). The primary difficulty involves the transformation of the oil and fats derived from these biomass sources into biofuels that are appropriate for use as a viable alternative to conventional fuel. Biofuels derived from biomass, namely lignocellulosic materials, frequently exhibit challenges related to their elevated viscosity, diminished energy content, and polyunsaturated nature.These concerns can be addressed through several pre-treatment techniques, with transesterification being the most feasible approach (Lee et al., 2019). Transesterification is a chemical process in which fats and oils undergo conversion into esters and glycerol, facilitated by the presence of catalysts. The physical attributes of the fatty acid methyl ester (FAME) generated would exhibit similarity to the commercially available petroleum fuel, while the by-product glycerol also possesses commercial significance (Lee et al., 2019). Factors like alcohol to oil molar fraction, stirring speed, temperature, microalgae cell wall, moisture, reaction time, and type of catalyst have an impact on the transesterification efficiency process (Karpagam et al., 2021).

7.5. Alcoholic fermentation

In alcoholic fermentation, yeast or bacteria convert biomass leftovers containing fermentable sugars into bioethanol. For instance, *Chlorella* sp., *Chlamydomonas* sp., *Scenedesmuss* sp., *Dunaliella* sp., and *Spirulina* sp. can store over 50 % of their dry weight in starch, glycogen, and cellulose. The raw materials for bioethanol production are complex polysaccharides. Hydrolysis is used to enzymatically reduce polysaccharides into monosaccharides before using them as food since microbes have metabolic difficulties consuming them. Most hydrolysis procedures use acid/alkali solutions and enzymes. Acid therapy is fast and cheap. However, an acidic environment may cause unwanted sugar conversions. Enzymatic therapy is effective and produces no by-products. However, enzymes are expensive and slow. Cell disruption improves pre-hydrolysis, effectiveness, and duration (Günerken et al., 2015). Alcohol with 10–15 % crude ethanol content must be concentrated by distillation (Bibi et al., 2017). Liquefaction, gasification, or microwave-assisted pyrolysis can turn solid residue into usable products. Genetic engineering approaches have been applied to microalgae strains to increase metabolite output or switch to alternative metabolites. Genetic engineering aims to convert CO_2 into biofuels through photosynthesis. This method saves energy by avoiding biomolecule synthesis and degradation for energy storage and cellular architecture. Photosynthesis produces glucose and other metabolites through the Calvin cycle. Ribulose-1, 5-bisphosphate and CO_2 react to produce two 3-phosphoglyceric acid molecules. These acids are glucose precursors (John et al., 2011). Many studies have tried to change 3-phosphoglyceric acid's molecular structure to produce ethanol. To reroute ethanol synthesis, pyruvate decarboxylase and alcohol dehydrogenase genes are introduced. One study created a recombinant *Rhodobacter* sp. strain that produced ethanol (Lee et al., 2019). The recombinant strain produced ethanol anaerobically in light.

8. Products from agro-industrial wastes

Sugarcane bagasse, wheat bran, rice bran, green gram, wheat straw, rice husk, soy hull, sago hampas, debris from grapevine trimmings, sawdust, corncobs, coir pith from coconut, banana waste, aspen pulp, palm oil waste, sugar beet pulp, apple, peanut meal, rapeseed cake, coconut oil cake, mustard oil cake, cassava flour, wheat flour, steamed rice, steam treated willow, starch, etc are some examples of agro-industrial wastes. On the other hand, wheat bran is the most frequently utilized in various operations (Naik et al., 2019). In the present circumstances the challenges faced globally are generation of profuse number of wastes and the depletion of fossil fuels along with the management of agricultural waste estimated to be 1000million tons (Guo et al., 2018). Conversion of these agricultural wastes into bio-based products could be an ecologically sound strategy to confront the cataclysm (Reisinger et al., 2013). The residues from agricultural production and processing unit of crops, poultry, dairy, livestock, vegetable and fruit wastes, agro industry is considered as agricultural wastes (Obi et al., 2016). Lignocellulosic biomass which are obtained from agricultural wastes and comprise of cellulose, hemicellulose and lignin that can be reprocessed as bioplastics or emergence of chemical compounds (Blasi et al., 2023).

8.1. Biofuel

The two major categories of liquid biofuel include ethanol and biodiesel. Ethanol is obtained by fermenting the sugars extracted from beet and sugarcane employing yeast or from the depolymerized starch of corn, cassava, and wheat. Biodiesel are generated from triglycerides of canola, soy, and oilseed or from mesocarp of palm fruits. The transesterification process of triacyl glycerol along with methanol to produce fatty acid methyl esters and glycerol is the basic conversion process for biodiesel (Youngs and Somerville, 2012).

8.2. Bioethanol

The world's substantial biofuel that can be considered as an alternative for gasoline and to transportation is bioethanol. It is a precursor and an organic solvent that mediate the synthesis of chemicals and composites (Ashokkumar et al., 2022). The production of first generation (1 G) biofuels were acquired through fermentation of yeast in

sucrose crops that were supposedly used for animal feed like grains (wheat, maize), tuber crops (sugar beet, potato) and sugarcane molasses (Hans et al., 2023). Second generation (2 G) bioethanol is produced from lignocellulosic materials that include solid waste, wood processing wastes, and non-food plants like switch grass and trees and agricultural residues (Robak and Balcerek, 2018). Third generation (3 G) bioethanol was extracted from algal biomass (Maliha and Abu-Hijleh, 2022).

8.3. Biodiesel

Biodiesel is generated from triglycerides of canola, soy, and oilseed or from mesocarp of palm fruits. The transesterification process of triacyl glycerol along with methanol to produce fatty acid methyl esters and glycerol is the basic conversion process for biodiesel (Youngs and Somerville, 2012). The conversion of lignocellulosic biomass into biodiesel has enormous potential as a sustainable and renewable replacement for fossil fuels. The production of biodiesel is restricted in many countries due to the requirement of land for the growth of oil seed crops and competing with traditional crops (Severo et al., 2019). Pre-treatment techniques that are chemical, physical, and biological have been investigated in an effort to cut through the complicated structures, increase the enzymatic hydrolysis effectively, and eliminate contaminants (Galbe and Zacchi, 2007). There have been proposals for integrated bio-systems to increase the efficiency of producing biodiesel from lignocellulosic biomass. These methods aim to generate high-value products along with biodiesel by optimizing the biomass components like lignin and hemicellulose. Pre-treatment of lignocellulosic biomass gives lignin as a by-product that can be valorized to produce biofuels, chemical or high-grade materials that cut down waste and increase the overall economic process (Hu and Ragauskas, 2012).

8.4. Bio-plastic

Bioplastics are those made from renewable sources which can be degraded. The expense of raw materials and microbial processing along with the prerequisite for purification following polymerization limits the ability of bioplastics to compete with petrochemical plastics. Furthermore, it is procurable to manufacture conventional biobased polymers like bio propylene and bio polyethylene which comprises of natural materials and bio-PET a polyethylene terephthalate typically uses only one natural material (Mujtaba et al., 2023). Polymers that are employed in long life applications include polyamides polymethylmethacrylate, and polyurethanes. They can be manufactured fractionally manufactured using itaconic acid by-product from the industrial fermentation of glucose. There have been efforts to extract itaconic acid from lignocellulosic biomasses like corn stover, wheat chaff, bamboo, wheat bran to make it less than 50 % to obtain. In contrast it is expensive to extract fermentable sugars from these biomasses (Kawaguchi et al., 2022). The utilization of agricultural waste derived lignocellulosic biomass to produce bioplastics could potentially reduce its cost and solve one of the major land related problems. Numerous nonedible sources like coffee husk, corn stover, pineapple leaf, spent coffee ground, coconut fiber, banana peels, corn cob, apple pomace, rice husk, sugarcane bagasse, mango peel, wheat straw and grape pomace have been explored as lignocellulosic feedstocks (Lu et al., 2022). Biodegradable plastics can be produced utilizing these raw materials which would curb the wastes, however there are few discussions that could be raised on this aspect (Goel et al., 2021). Manufacturing of synthetic plastics using petroleum-based chemicals threaten environmental sustainability owing to its limitation in fossil fuel and polymers originated from petroleum are resistant to degradation by intrinsic organisms in nature (Patermann and Aguilar, 2018). Immense efforts were invested in conversion of agricultural wastes to Polyhydroxyalkanoates (PHA) which is a promising route for waste valorisation (Amulya et al., 2016). In the present circumstances bioplastics from poly lactic acid (PLA) are more prevalent in the market and the application of PHA is under initial stage for commercialization (Liguori and Faraco, 2016). PHA also includes Polyhydroxybutyrates (PHB) and polyhydroxy valerate (PHV). Later to the fermentation of available sugars, few bacteria generate and use them as carbon energy. Further research on wastes like spent cooking oil, maize stover, milk whey, rice husks, starchy effluent from processing of cassava, rice husks have sparked due to the cost of biobased and biodegradable polymers (Chavan et al., 2022). The recycling of biodegradable and non-biodegradable plastics have raised concerns as they have increased in production and diversity. To obtain high quality and feasible recycling the biodegradable polymers composed of agricultural and non-agricultural wastes need to be separated. In the recycling streams PLA, which is a biodegradable plastic should be the target among the biodegradable plastics produced (Fredi and Dorigato, 2021).

8.5. Enzymes

In light of the vast range of biological, scientific and industrial application for enzymes there has been a significant increase in curiosity regarding them globally. Widely spread natural enzymes have been utilized in the creation of goods including cheese, wine beer, and vinegar, as well as manufacturing of leather, indigo, linen and other materials (Naik et al., 2023). Food waste is an inexpensive source of lignocellulosic biomass that are utilized to produce wide range of enzymes that include cellulase, invertase, xylanase, protease, β-xylosidase, lipase, pectinase, mannanase, inulinase, phytase, amylase, polygalacturonase, β-glucanase, transglutaminase (Ravindran and Jaiswal, 2016a). Enzymatic hydrolysis is the pretreatment followed lignocellulosic treatment of food wastes. Few fungal organisms like *Scytalidium termophilum*, *Aspergillus* sp., *Melanocarpus* sp., do not require enzymatic hydrolysis (Ravindran and Jaiswal, 2016b).

8.6. Bio-hydrogen

Microorganisms, mainly photosynthetic bacteria and some archaea, ferment organic resources to produce biohydrogena clean and sustainable energy source. As a consequence of their activity, these microbes create hydrogen gas, which is a green and renewable energy source (Ahmed et al., 2021). The variety of intermediates and by-products that biohydrogen synthesis generates increases its value. These include materials that may be further processed to produce a variety of bio-based products, such as organic acids, volatile fatty acids, and alcohols. Volatile fatty acids, for example, can be converted into biofuels or bioplastics, which will help the bioeconomy and lessen the environmental impact of many businesses. This procedure not only increases the biohydrogen production's economic viability but also promotes the use of waste materials, which lessens its negative environmental effects (Ahmed et al., 2021). An advanced biofuel that is clean, carbon free and nontoxic attained via thermochemical and biological processes. The energy content is 120 to 142.9 MJ/Kg with a calorific value of 143GJ/ton which makes it preferable over other biofuels (Awogbemi and Kallon, 2022). For its profuse industrial applications an increase in biohydrogen consumption by 8–10 % within 2025 can be anticipated (Kumar Gupta et al., 2013). For by-productshydrogen production microbes are the vital organisms that are involved in metabolic activities which increase the efficiency of soil wastes. The recovery of biohydrogen was done during the process of fermentation.

9. Bio-based product development and commercialisation

In the current times countries are working on the employing food wastes as fuels. Countries like Denmark, Finland and Sweden are utilizing agricultural and food wastes like bakery waste, fruit and vegetable wastes, household biowaste, animal waste, agricultural waste to investigate into new technologies and convert them to biofuels (Food Waste to Biofuels – Nordic Energy Research, 2019).

Several studies have been carried out for the recovery of enzymes

from food waste and by products according to the literature As an example, the production of α-amylase from the wastes of coffee with the help of solid-state fermentation using a fungal strain *Neurospora crassa* (CFR 308) along with glucoamylase derived through food waste using submerged fermentation together with *Aspergillus niger* UV-60, coupled with laccase obtained from melon waste through solid state fermentation using *Bacillus coagulans* were revived (Capanoglu et al., 2022). An example of innovative biotechnology is the usage of varied species of insect for the valorization of residual biomasses. These insects can utilize the nutrients of the organic wastes in their bodies that could create homogeneous biomass which is inestimable (Leni et al., 2021). Bio-treatment of food waste using a black soldier fly larva (*Hermitia illucens*) contributes to the reduction of volume in food waste and provides a high quality of animal feed. These larvae can derive benefits from waste as a constituent of grass fertilizer and animal feed (Magee et al., 2021).

10. Assessment of environmental and economic benefits

The common practice in most of the developing countries is the burning of the crop residues especially in Asia. A study conducted states that ethanol from corn degrade water quality rapidly. However cellulosic ethanol has a less impact than on corn whereas it relies on fertilizers for its growth (Dey et al., 2021). Regarding the cost benefit analysis using nanoparticle based fertilizers there aren't many research in the literature. Although current nano formulations have an abundance of potential for reducing environmental impact and raising the net revenue from crops, wide scale use of these formulations will require a significant enhancements (Kaur et al., 2023). At present there are several obstacles that prevent the utilization of alternative fuels. The availability of traditional fossil fuel makes it challenging for alternative fuels to meet the cost-effective production prices. The quality in production is a key problem with biofuels and waste fuels. The commercial biofuels that are in the market cannot be explicitly used due to their decrease in heating value, lower thermal stability, increased acidity etc. However extensive research is being carried out in this field and the fuels being produced are refining and their usage in future is of no doubt (Markov et al., 2021). Lignocellulosic biorefinery is one of the majorly studied refinery approach for ethanol and electricity for their economic feasibility and environmental impact. In this method of biorefinery, the structural carbohydrates of the agricultural wastes are converted to monomers of sugars and thereafter fermented to produce ethanol, lignin and the other unfermented products are burned to generate heat and electricity (Awasthi et al., 2019). Conversion of unfermented components to biogas by a process of anaerobic digestion in the whole stillage is one of the high potential biorefinery processes for agricultural waste (Kumar and Singh, 2018).

11. Sustainability considerations of biorefinery

The bio-revolution represents a profound paradigm shift in the fields of industry and technology, where the conventional sources of fuels, plastics, and chemicals are supplanted by plant-based alternatives. This visionary transition signifies a transformative relationship with nature, driven by the sustainable utilization of agricultural feedstock's (Konwar et al., 2018). At its core, the bio-revolution entails the conversion of these feedstock's into a diverse range of biofuels (Tsegaye et al., 2021), bioplastics, biochemical's (Bauer et al., 2018), and an array of other bio-based products. This forward-thinking approach holds the potential to substantially reduce humanity's dependency on finite fossil fuel resources, fostering a future characterized by environmental harmony and resource sustainability (Donner and de Vries, 2021).

The dynamic growth of bio-revolution is fuelled by scientific breakthroughs, cutting-edge technologies, and an increasing global awareness of environmental sustainability (Donner and de Vries, 2021). Advanced biotechnological methods, including genetic engineering, are instrumental in optimizing the conversion of agricultural feedstocks (Konwar et al., 2018) into valuable bio-based products, enhancing crop yields, and refining bioconversion processes. The bio-revolution continuously introduces innovative bio-based products, spanning biodegradable plastics, sustainable chemicals, bio-based lubricants, and advanced materials. These innovations not only address diverse industrial needs but also uphold the principles of environmental responsibility and resource conservation (Bauer et al., 2017). As the bio-revolution gains momentum, the burgeoning consumer demand for sustainable products propels market expansion (Ronzon et al., 2020) in the bio-based sector. This heightened interest fosters investments and innovations while contributing to economic growth. The bio-revolution stands as a testament to human ingenuity and a shared commitment to reducing our reliance on finite fossil fuels, while fostering a future where sustainability (Donner and de Vries, 2021) and ecological equilibrium will reign supreme. In doing so, it offers hope for a world where humanity and nature coexist in a mutually beneficial relationship, driven by innovation and environmental stewardship (Bauer et al., 2018).

Now, imagine taking a journey through the life of a product, from the moment it's conceived to the day it's recycled or disposed of. This journey is precisely what Life Cycle Analysis (LCA) offers **(**Fig. 3**)** a scientific voyage that explores the sustainability of bio-based products (Donner and de Vries, 2021) in a comprehensive way. Therefore, LCA is like a powerful compass for sustainability (Donner and de Vries, 2021), guiding us to make informed decisions about bio-based products. It's a rigorous methodology that considers every stage of a product's life, from its birth to its environmental impact and eventual fate. LCA doesn't just look at a single aspect; it examines the intricate interplay of environmental, economic, and social factors, offering a 360-degree view of a product's influence on the world around us.

LCAs provide data-driven insights, continuously informing improvements to reduce the environmental impact of biorefinery operations (Conteratto et al., 2021) and plays a major role in minimize the carbon and ecological footprint of biorefinery operations, as this approach involves several strategic measures. Starting from careful feedstock selection (Konwar et al., 2018) and sustainable land management practices are essential, favouring locally suited, fast-growing crops and precision agriculture. Advanced, energy-efficient conversion technologies like enzymatic hydrolysis reduce waste generation (Maina et al., 2017) and energy consumption. Carbon Capture and Storage (CCS) technology captures and securely stores CO_2 emissions, mitigating greenhouse gas impacts (Solis et al., 2020). Efficient water management, including recycling and purification, minimizes water use and ecological harm. Biodiversity conservation measures (Sillanpää and Ncibi, 2017), such as preserving natural habitats and conducting ecological assessments, help protect local ecosystems. Waste valorisation strategies transform waste streams (Maina et al., 2017) into valuable products, enhancing resource efficiency. These scientifically grounded strategies collectively contribute to the sustainability and responsible environmental stewardship of biorefineries, ensuring they produce valuable bio-based products with minimal ecological and carbon footprint. These strategies are vital for ensuring that biorefineries can contribute to a more sustainable and environmentally responsible future while producing valuable bio-based products (Donner and de Vries, 2021). In recent years, there has been a significant increase in the use of microalgae for the production of bio-based goods. The use of microalgae biorefinery for protein and energy production has the potential to effectively address hunger and meet energy needs, especially in emerging and least-developed countries. Future research on utilizing algal biomass in CBE focuses on several key objectives (Ramos Huarachi et al., 2023). These include developing methods for conducting large-scale operations, enhancing the value of algal-based products, and addressing the challenges posed by price uncertainty and demand fluctuations. In addition, it is important to take into account social and economic factors when conducting related assessments. The treatment

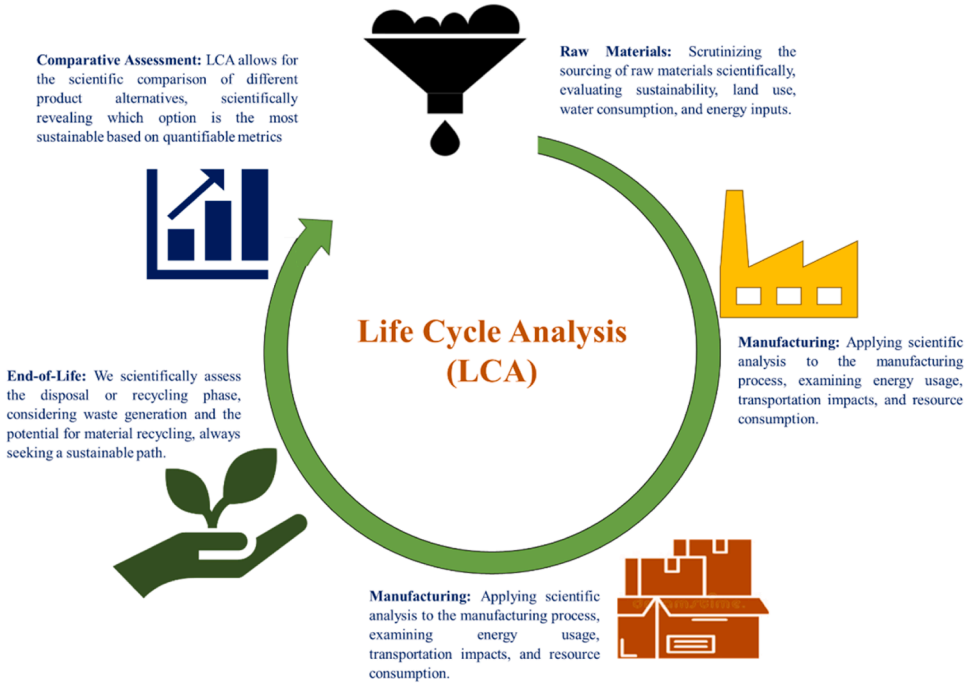

Fig. 3. Life Cycle Analysis (LCA) of bio-based products.

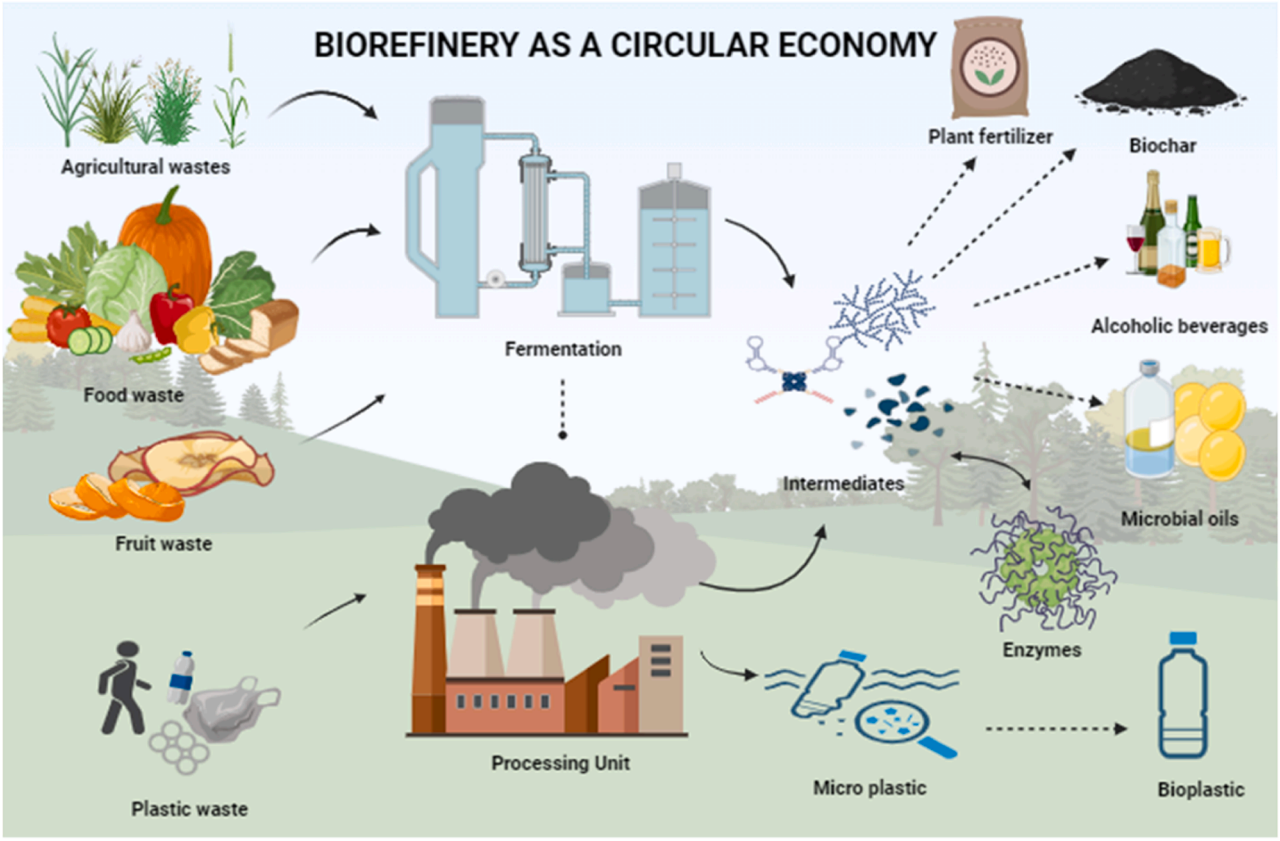

Fig. 4. Bio-refineryas a circular economy.

of wastewater presents a great opportunity for CBE to capitalize on. Wastewater, which can come from industrial or home sewage, is a continuous input that is commonly treated through anaerobic digestion (Calicioglu et al., 2021). This process allows for the recovery of biogas and biofertilizers. Further research is needed to investigate different approaches for treating wastewater. It is also important to explore alternative materials that can be treated with wastewater. Additionally, risk management strategies should be considered. Moreover, efforts

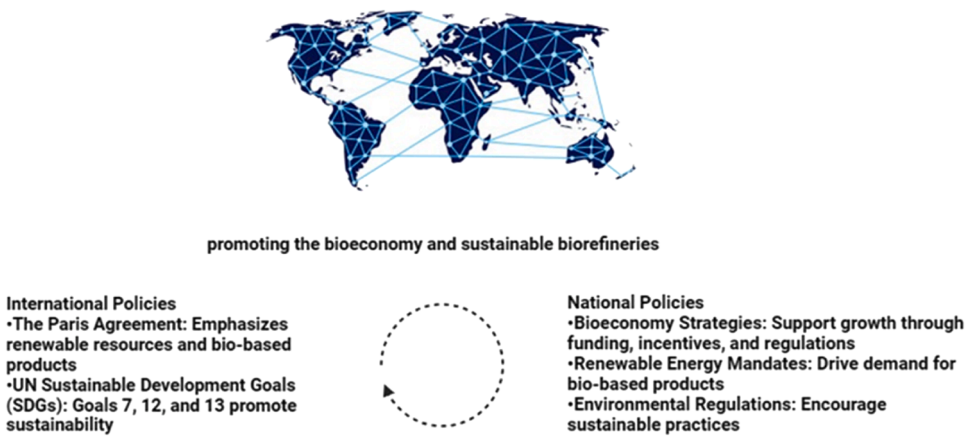

Fig. 5. International Policies and National Policies.

should be made to develop more valuable products from wastewater, such as single-cell proteins. Using animal waste in a controlled biological environment (CBE) is a strategic approach because it has a significant negative impact on the environment (Ramos Huarachi et al., 2023). One notable example of environmental impact is the emission of large amounts of methane from dairy manure. As a result, a common approach in CBE is to use animal dung and waste to produce valuable products that offer enhanced benefits (Freitas et al., 2021). These include biofuels such as biodiesel or biogas, as well as the conversion of biomass into animal feed. In a bioeconomy, bioproducts are any products that are derived from biomass. The main objective of a CBE is to create bioproducts that have a high level of added value. These bioproducts can include biochemicals, bio-based proteins, or biopolymers (Karpagam et al., 2021). The field is currently trending towards methods that allow for the acquisition of higher-value goods that are technologically advanced, cost-effective, and environmentally sustainable. Biowastes show great potential as a viable resource for generating bioenergy (Freitas et al., 2021). Biorefinery techniques are used to extract bioenergy from biowastes, also known as waste-to-energy. There are several methods used for heating and electricity generation, including combustion, trans-esterification, and anaerobic digestion (Ramos Huarachi et al., 2023). Combustion provides immediate heating and electricity. Trans-esterification is used to produce biodiesel. Anaerobic digestion is particularly effective for producing biogas, which can be used for heating and electricity applications. Researchers are currently investigating ways to maximize the value of biofuels and develop more environmentally friendly techniques in the field of bioproducts. Circularity is an inherent characteristic of CBE. The CBE has established a connection between the bioeconomy and the circular economy, highlighting their interdependence (Bi et al., 2022; Gatto and Re, 2021; Patel et al., 2016; Ramos Huarachi et al., 2023; Rodionova et al., 2022). Currently, research trends are centredon exploring new methods to reuse materials and energy in integrated models. There is also a focus on enhancing technology and processes to create feedback loops (Calicioglu et al., 2021). Additionally, researchers are working on developing alternative recycling models in agriculture and analysing the environmental impacts of recycled products compared to market-substituted products (Ramos Huarachi et al., 2023). Finally, efforts are being made to optimize the efficiency of product cascading. The integration of life cycle assessments (LCAs) with economic evaluations has been proposed through the use of life cycle costing (LCC) methodology (Kaur et al., 2023). The techniques used in this approach follow the conventional unit-cost method at every stage of the value chain (Ramos Huarachi et al., 2023). They also take into account the impact on social welfare caused by exchanges that are usually overlooked, known as externalities (Carvalho et al., 2020). In bio-based value chains, the consolidation of budgetary expenses, transfers, and external factors at each stage of the biomass supply and value chain allows for the identification of corresponding physical and economic criteria (Sevigné-Itoiz et al., 2021).

12. Waste reduction and circular economy

Imagine a biorefinery equipped with cutting-edge enzymatic technologies (Conteratto et al., 2021). Scientifically designed enzymes break down agricultural residues, such as corn stover and wheat straw, into sugars and biofuels (Tsegaye et al., 2021). These processes, grounded in scientific understanding, efficiently convert waste into valuable resources, supporting a circular economy (Kircher, 2021; Maina et al., 2017). The scientific foundation of this approach not only minimizes waste but also mitigates the environmental impact associated with waste disposal. Through scientific innovation and resource optimization, biorefineries pave the way for a more sustainable, waste-reduced, and circular future, where the concept of "waste" evolves into a source of opportunity and resource abundance. So, biorefineries stand as exemplars of sustainable innovation (Bauer et al., 2018), playing a pivotal role in reshaping our approach to waste reduction and the establishment of a circular economy (Kircher, 2021). Their scientific contributions to converting bio-waste into valuable resources embody a fundamental shift in how we view and utilize organic waste streams (Duan et al., 2020), fostering a harmonious relationship between economic growth and environmental stewardship. Thus, agro-industry is undergoing a profound transformation as it embraces closed-loop systems designed to minimize waste generation (Maina et al., 2017), reduce environmental impact, and optimize resource utilization. This comprehensive review delves into the scientific strategies that are reshaping agricultural practices, fostering sustainability (Donner and de Vries, 2021) and ushering in a circular approach to food production (Sillanpää and Ncibi, 2017). Closed-loop systems within the agro-industry are increasingly shaped by scientific strategies that prioritize sustainability (Donner and de Vries, 2021), resource efficiency, and environmental stewardship. These scientifically informed approaches minimize waste generation (Maina et al., 2017), optimize resource utilization, and pave the way for a more sustainable and circular agricultural system and pave the way for a more sustainable and circular agricultural system (Kircher, 2021).

12.1. Key features of waste reduction and circular economy

12.1.1. Precision agriculture and data-driven decision-making

A cornerstone of closed-loop agriculture is precision agriculture, grounded in cutting-edge technologies like GPS, sensors, and remote sensing. These scientific tools provide real-time data on soil conditions, crop health, and weather patterns. By harnessing this wealth of information, farmers can make data-driven decisions; optimizing resource

use and minimizing waste (Maina et al., 2017) within a closed-loop systematize a scientifically managed farm where precision agriculture technologies provide real-time data on soil conditions and crop health. This data guides data-driven decisions on water use, fertilizer application, and pest control, ensuring optimal resource utilization. Crop residues are scientifically converted into bio-based products, while livestock waste is used for biogas production and organic fertilizers (Duan et al., 2020). These scientifically driven practices minimize waste, reduce environmental impacts, and maximize resource efficiency within a closed-loop system, exemplifying the transformative potential of scientific strategies in agriculture (Maina et al., 2017).

12.1.2. Sustainable crop rotation and diversification

Scientifically guided crop rotation and diversification strategies are pivotal for soil health and reducing the need for synthetic inputs. Scientific research informs the selection of compatible crop combinations and timing, thereby reducing the risk of pests and diseases while promoting more robust ecosystems. Scientifically designed crop rotations, including legumes, enhance soil fertility, thus furthering the goals of a closed-loop system (Briassoulis et al., 2021).

12.1.3. Efficient water management

Nutrient bioactive compounds are abundant in agricultural waste and leftovers. For the industrial processes, these waste such as minerals, carbohydrates, proteins, should be considered as raw material rather than wastes due to their diverse composition (Naik et al., 2023). Scientifically designed water management systems are fundamental to closed-loop agriculture. Precision irrigation, water recycling, and data-driven decision-making enable optimal water use, reducing waste and conserving this precious resource (Maina et al., 2017). Scientific monitoring of soil moisture levels and plant needs ensures precise watering, resulting in both water conservation and minimized environmental impact (Sillanpää and Ncibi, 2017).

12.1.4. Biomass utilization and circular economy

Within a closed-loop system, agricultural waste (Maina et al., 2017), such as crop residues and by-products, is transformed into valuable resources through advanced techniques like anaerobic digestion or thermochemical processes (Bauer et al., 2018). Scientifically informed biomass utilization (Conteratto et al., 2021) not only reduces waste but also generates valuable biofuels (Tsegaye et al., 2021), bio-based products, and organic fertilizers, thus contributing to a circular economy (Kircher, 2021).

12.1.5. Scientific livestock management

Livestock integration within closed-loop agriculture is meticulously managed using scientific insights. Livestock waste (Maina et al., 2017), for instance, can be scientifically converted into biogas or nutrient-rich compost, contributing to both energy production and soil enrichment. Scientifically informed animal husbandry practices emphasize feed efficiency and reduced environmental impacts.

12.1.6. Integrated pest and disease management

Scientifically based integrated pest and disease management practices prioritize natural predators, precise crop monitoring, and targeted pesticide application. This approach minimizes environmental damage while maintaining crop yields within a closed-loop agricultural system.

12.1.7. Soil health enhancement

Scientifically informed soil health practices, including cover cropping and no-till farming, bolster soil structure, reduce erosion, and sequester carbon. These practices scientifically enhance the resilience of agricultural ecosystems while minimizing waste and resource depletion (Maina et al., 2017).

13. Global transition towards a sustainable bioeconomy

The global transition towards a sustainable bioeconomy (Donner and de Vries, 2021) has gained immense momentum in recent years, driven by the pressing need to address climate change, resource scarcity, and environmental degradation (Gawel et al., 2019). This paradigm shift represents a holistic approach to harnessing the potential of biological resources to create value-added products while simultaneously mitigating the negative impacts of traditional industries. At both international and national levels, policies and initiatives have been devised to promote and guide the development of bioeconomies, with a particular focus on sustainable biorefineries (Donner and de Vries, 2021) as key drivers of this transformation. On the international stage, organizations such as the United Nations and the European Union have been at the forefront of promoting bioeconomy policies. The United Nations Sustainable Development Goals (SDGs) prominently feature bioeconomy-related targets, recognizing the vital role of bio-based resources in achieving a sustainable future. Specifically, SDG 12 calls for responsible consumption and production, with an emphasis on promoting the efficient use of natural resources, reducing waste generation (Maina et al., 2017), and supporting the development of sustainable production methods, including biorefinery processes. Within the European Union, the European bioeconomy strategy has laid out a comprehensive framework for the development of a circular and sustainable bioeconomy (Kircher, 2021). This strategy encompasses various policy instruments, such as research funding, regulatory measures, and public-private partnerships, all aimed at fostering the growth of biorefinery industries (Conteratto et al., 2021). By aligning regional and national policies with these international initiatives, member states of the EU have made substantial progress in promoting sustainable biorefineries and bioeconomy development (Donner and de Vries, 2021). At the national level, countries around the world have recognized the potential economic and environmental benefits of bioeconomy development (Gawel et al., 2019). For instance, countries like Finland and Brazil have embraced bioeconomy as a strategic priority, channelling significant investments into research, development, and innovation in biorefinery technologies (Bauer et al., 2018). These national policies aim to not only reduce greenhouse gas emissions (Solis et al., 2020) but also create new opportunities for rural development and job creation (Ronzon et al., 2020) particularly in agriculture and forestry-dependent regions. Moreover, governments have introduced regulatory measures and incentives to encourage the transition towards sustainable biorefineries. Tax credits, subsidies, and grants have been implemented to support the construction and operation of biorefineries, reducing the financial barriers associated with adopting these environmentally friendly technologies. Simultaneously, stricter environmental regulations have been put in place to limit the environmental impact of conventional industries, further incentivizing the adoption of sustainable alternatives (Donner and de Vries, 2021). Commercial production in the context of sustainable biorefineries has witnessed a remarkable surge due to these policy initiatives. Biorefineries enable the conversion of various biomass feedstocks (Conteratto et al., 2021), such as agricultural residues, algae (Solis et al., 2020), and woody biomass, into a plethora of valuable products, including biofuels (Tsegaye et al., 2021), bioplastics, biochemicals (Bauer et al., 2018)., and bio-based materials. As these facilities become more economically viable and efficient, they play a pivotal role in diversifying the industrial landscape, reducing dependency on fossil resources, and contributing to the circular economy (Kircher, 2021). The global shift towards a bioeconomy (Gawel et al., 2019) driven by sustainable biorefineries is being actively promoted through a combination of international and national policies. These policies not only address the urgent need to mitigate climate change and reduce environmental degradation but also recognize the economic opportunities presented by the bioeconomy (Gawel et al., 2019). The convergence of these efforts fosters innovation (Bauer et al., 2018), investment, and commercial production in sustainable biorefineries,

thereby paving the way for a more sustainable and prosperous future (Donner and de Vries, 2021).

14. Analysis of market trends and consumer demand for bio-based products

The global landscape for bio-based products has witnessed significant shifts in recent years, driven by evolving market trends and changing consumer demands (Ronzon et al., 2020). This analysis delves into these dynamics, highlighting the challenges and opportunities inherent in scaling up biorefinery processes for commercial production (Conteratto et al., 2021).

14.1. Key points from analysis of market trends and consumer demand

14.1.1. Market trends

- Growing sustainability awareness among consumers and businesses (Ronzon et al, 2020; Ronzon et al., 2020)
- Stringent legislation and regulations driving the adoption of eco-friendly practices
- Emphasis on circular economy (Kircher, 2021) principles, promoting products with reduced environmental impact
- Continuous advancements in biorefinery processes and technologies, expanding the range of bio-based products (Conteratto et al., 2021)

14.1.2. Consumer demand

- Consumers making sustainable choices, favouring bio-based products (Donner and de Vries, 2021)
- Increased demand for safer and healthier products, especially in sectors like cosmetics and food packaging (Sillanpää and Ncibi, 2017)
- Greater importance placed on product transparency and sustainability certifications (Donner and de Vries, 2021)

14.1.3. Challenges in scaling up processes

- Economic viability at a larger scale, requiring substantial investment in infrastructure and technology
- Ensuring a consistent and sustainable supply of feedstock for biorefineries (Konwar et al., 2018)
- Complex and costly regulatory compliance at a commercial scale

14.1.4. Opportunities

- Diversification of product portfolios to cater to various markets and adapt to changing demands (Ronzon et al., 2020)
- Fostering innovation through collaboration with research institutions and industry partners (Bauer et al., 2018)
- Enhancing market presence through certifications and aligning with market trends (Ronzon et al., 2020)

15. Exploring uncharted territories: research frontiers of bioeconomy

In the realm of biorefinery processes (Conteratto et al., 2021), there exists a pressing need to overcome substantial technological challenges while simultaneously exploring exciting research frontiers to realize the full potential of sustainable resource utilization (Donner and de Vries, 2021). These challenges are multifaceted, starting with the diverse array of feedstocks, each bearing unique characteristics. Tackling this issue requires the development of effective pretreatment methods, particularly in breaking down complex lignocellulosic materials (Konwar et al., 2018) into their usable components, such as sugars and lignin. Moreover, the quest for efficient and cost-effective conversion methods, encompassing enzymatic hydrolysis and fermentation, remains a paramount challenge. The goal is to maximize yields of target products while minimizing the generation of by-products. Equally critical is the optimization of microbial strains and enzyme cocktails for specific biorefinery applications (Conteratto et al., 2021). Achieving the stability, productivity, and substrate range required for diverse feedstocks and products is an ongoing pursuit (Konwar et al., 2018). Additionally, the effective management and utilization of waste streams and residues generated during biorefinery processes represent an imperative challenge (Conteratto et al., 2021). This involves innovative approaches, such as the development of novel by-product applications, where substances like lignin can find new life as valuable chemicals. The separation and purification of products within biorefineries are essential, necessitating the application of advanced techniques like membrane technology and chromatography. Scaling up from laboratory-scale operations to commercial-scale biorefineries presents its set of engineering challenges, demanding the seamless integration of various unit operations while maintaining economic viability. Furthermore, the pursuit of biorefinery processes (Conteratto et al., 2021) that are both energy-efficient and environmentally sustainable stands as a fundamental challenge. It involves minimizing energy inputs, mitigating greenhouse gas emissions (Solis et al., 2020), and minimizing waste generation throughout the entire process (Maina et al., 2017). On the horizon of research frontiers, promising areas beckon. Advances in biological and synthetic biology hold the potential to engineer microorganisms and enzymes, thereby enhancing their performance and expanding their substrate utilization range. Meanwhile, novel pre-treatment methods, such as those involving ionic liquids and deep eutectic solvents, are emerging as environmentally friendly and efficient alternatives. The exploration of new applications and markets for co-products (Ronzon et al., 2020)generated during biorefinery processes (Conteratto et al., 2021), including lignin-based materials and specialty chemicals, offers exciting avenues for innovation (Bauer et al., 2018). Advanced process modelling and simulation techniques are enhancing the optimization of biorefinery processes, facilitating efficient process design and scale-up. The integration of biorefineries into circular economy (Kircher, 2021)models, where waste and by-products (Maina et al., 2017) become valuable resources for other industries, represents a transformative frontier. Hybrid biorefinery concepts (Conteratto et al., 2021), which combine multiple feedstocks and conversion pathways (Konwar et al., 2018), promise to maximize resource utilization and product diversity. Meanwhile, the development of comprehensive sustainability assessment metrics (Donner and de Vries, 2021), including life cycle analysis, allows for the quantification of the environmental, economic, and social impacts of biorefinery processes. Lastly, the pursuit of biorefinery resilience strategies, capable of safeguarding against external factors such as climate change and supply chain disruptions, remains critical. Navigating these technological challenges and actively exploring research frontiers will be instrumental in harnessing the full potential of biorefinery processes (Conteratto et al., 2021). As science and engineering continue to advance in these areas, biorefineries are poised to play an increasingly pivotal role in sustainable resource utilization (Donner and de Vries, 2021)and the broader transition towards a bio-based economy.

16. Conclusions and future perspectives

The bioeconomy is a dynamic and progressive domain that integrates scientific advancements, policy frameworks, and innovative practices with the aim of fostering a sustainable trajectory for the future. The bioeconomy is propelled by significant factors, including heightened environmental consciousness and economic prospects. Within this context, agriculture and agro-industry assume a crucial function by supplying raw materials and transforming them into valuable commodities. Biorefineries, employing novel methodologies to fully exploit the inherent capabilities of feedstocks, assume a pivotal role in

facilitating the ongoing environmental transformation. The bioeconomy demonstrates its potential for sustainable innovation by its adeptness in extracting value-added products and derivatives from biomass, hence optimizing the utilization of existing resources. The idea of sustainability serves as a guiding framework for stakeholders in the field of bioeconomy, with the aim of minimizing waste and maximizing the utilization of resources. Nevertheless, the bioeconomy encounters various obstacles and unexplored domains. The persistence and dynamism of the movement are sustained by technological hurdles and ongoing research endeavours, which continuously expand the horizons of bioeconomic growth. The bioeconomy and biorefineries exemplify humanity's ability to generate, adjust, and invent, showcasing the potential to extract valuable resources from the Earth's fertile lands through the adoption of sustainable practices. This approach fosters a balanced and prosperous future for future generations.

The bioeconomy is a dynamic and progressive field that brings together scientific advancements, policy frameworks, and innovative practices to promote a sustainable future trajectory. Two main factors-increased environmental awareness and promising economic opportunities-drive the bioeconomy. In this context, agriculture and the agro-industry play a crucial role. They provide raw materials and then transform them into valuable commodities. Biorefineries play a crucial role in the ongoing environmental transformation by utilizing innovative methods to fully maximize the potential of feedstocks. The bioeconomy showcases its ability to drive sustainable innovation by efficiently extracting valuable products and derivatives from biomass. This optimizes the use of available resources and demonstrates its potential for long-term sustainability. The concept of sustainability is a guiding principle for stakeholders in the field of bioeconomy. Its main objective is to minimize waste and maximize the utilization of resources. However, the bioeconomy still faces numerous challenges and areas that have yet to be fully explored. Technological hurdles and ongoing research endeavors sustain the persistence and dynamism of the movement, constantly expanding the horizons of bioeconomic growth. The bioeconomy and biorefineries demonstrate humanity's capacity to generate, adapt, and innovate by extracting valuable resources from the Earth's fertile lands through sustainable practices. This approach promotes a future that is both balanced and prosperous for generations to come.

CRediT authorship contribution statement

Conceptualization, B.M., Y.K.M. and A.K.M.; Data curation: M.S.W, S.S., and P. C.N,; writing-original draft preparation, M.S.W, S.S., and P. C.N; writing-review and editing, A.C., R.A.B.M., A.K.M. and Y.K.M.; visualization, Y.K.M. and A.K.M; image preparation, S.S., resources and software, B.M. and Y.K.M. All authors have read and agreed to the published version of the manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Review

Recent advances in cellulose-based sustainable materials for wastewater treatment: An overview

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ABSTRACT

Water pollution presents a significant challenge, impacting ecosystems and human health. The necessity for solutions to address water pollution arises from the critical need to preserve and protect the quality of water resources. Effective solutions are crucial to safeguarding ecosystems, human health, and ensuring sustainable access to clean water for current and future generations. Generally, cellulose and its derivatives are considered potential substrates for wastewater treatment. The various cellulose processing methods including acid, alkali, organic & inorganic components treatment, chemical treatment and spinning methods are highlighted. Additionally, we reviewed effective use of the cellulose derivatives (CD), including cellulose nanocrystals (CNCs), cellulose nano-fibrils (CNFs), CNPs, and bacterial nano-cellulose (BNC) on waste water (WW) treatment. The various cellulose processing methods, including spinning, mechanical, chemical, and biological approaches are also highlighted. Additionally, cellulose-based materials, including adsorbents, membranes and hydrogels are critically discussed. The review also highlighted the mechanism of adsorption, kinetics, thermodynamics, and sorption isotherm studies of adsorbents. The review concluded that the cellulose-derived materials are effective substrates for removing heavy metals, dyes, pathogenic microorganisms, and other pollutants from WW. Similarly, cellulose based materials are used for flocculants and water filtration membranes. Cellulose composites are widely used in the separation of oil and water emulsions as well as in removing dyes from wastewater. Cellulose's natural hydrophilicity makes it easier for it to interact with water molecules, making it appropriate for use in water treatment processes. Furthermore, the materials derived from cellulose have wider application in WW treatment due to their inexhaustible sources, low energy consumption, cost-effectiveness, sustainability, and renewable nature.

Abbreviations: AA, Acrylic acid; CD, Cellulose derivatives; CNC, Cellulose nano-crystals; CNF, Cellulose nano-fibrils; BNC, Bacterial nano-cellulose; NFC, Nano fibrillated cellulose; BC, Bacterial cellulose; SEM, Scanning electron microscope; IPC, Interfacial polyelectrolyte complex; HEC, Hydroxyethyl cellulose; DP, Degree of polymerization; MFC, Micro fibrillated cellulose; MCC, Microcrystalline cellulose; MO, Methyl orange; NC, Nanocomposites; NFs, Nanofibers; DS, Degree of substitution; Lys, Lysine; GMA, Glycidyl methacrylate; AM, Acrylamide; LbL, Layer-by-layer; S-NPs, Silicon nanoparticles; Ag-NPS, Silver nanoparticles; PEG, Polyethylene glycol; NDNP, Nanodiamond nanoparticles; RT, Room temperature; EDTA, Ethylenediaminetetraacetic acid; MS, Molecular substitution; PVA, Polyvinyl alcohol; NMMO, *N*-methyl morpholine-N-oxide; AMIMCl, 1-allyl-3-methyllimidazolium chloride; EMIMAc, 1-allyl-3-methyllimidazolium acetate; UDPGIc, Uridine diphosphoglucose; HPC, Hydroxypropyl cellulose; MC, Methyl cellulose; WW, Waste water.

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1. Introduction

Water is essential for human beings and is necessary for all other forms of life to survive. However, during the past 20 years, as a result of the rise of the economy, quick industrial development, urbanization, and agricultural development have led to water pollutions which is considered a serious global issue [1]. Water pollution occurs in many different ways, but one particularly terrible form is oil-water pollution, which occurs when wastewater containing oil is dumped into natural water bodies from various sources, including the food and petrochemical industries, daily living, and sewage treatment plants. Due to heavy metal ions' inability to degrade, tendency to cause cancer, and high toxicity, the pollution of water with heavy metal ions has been also a burning issue in recent years [2]. Another unpleasant form of pollution that comes from various industrial sectors, including the textiles, plastics, paint, cosmetics, and paper manufacturing industries is mainly caused by dyes [3]. By the end of 2010, >700,000 tons of dyes had been manufactured, and there are currently about 100,000 commercial dyes known to exist [4]. Sewage treatment poses a significant environmental and economic challenge today.

Although some materials with thorough study can be utilized to purify water quickly and effectively, not all materials are affordable and environmentally friendly. They have not been successfully used in the treatment of huge amounts of wastewater. Therefore, there is a pressing need to create some eco-friendly and effective water treatment materials. These materials must also be simple to use, highly active or efficient, and environmentally benign. Although their uses need more research, biodegradable biomass materials can be viewed in this light as viable candidates for use in practical water treatment systems. A rapidly expanding field of study called biodegradable biomass as a raw material offers wider applications for wastewater treatment. The biomass materials obtained from plants include forest derive waste, agricultural wastes, aquatic weeds, etc. [5]. It offers a potential option for practical water treatment due to its repeatability and degradability. Pollutants that harm both the environment and humans include textile dyes, heavy metal ions, and oil stains which are present in wastewater discharges [6]. For instance, heavy metal ions have been linked to a number of illnesses, including cancer. Dye-containing wastewater can make water bodies less clear and deplete the O_2 in the water, which stunts the survival of aquatic flora and microbes. Because of their diversity and simplicity of modification, optimal biomass concentrations are therefore particularly suitable for the elimination of these toxic pollutants. The biomass material can be altered which is a contribution from numerous researchers who also contribute to the creation of cutting-edge water treatment techniques that can be customized to meet particular requirements for the efficient removal of toxins from the wastewater. In the current situation, there is a lot of interest in finding a sustainable approach for the remediation of water contaminants [7].

A common macromolecule found in biomass is cellulose, a polymer of linear polysaccharide made up of β-1, 4-linked glucose units. Organic and inorganic pollutants are removed from wastewater using naturally obtained and modified groups of cellulose substances. However, in order to compete with competing materials for the WW treatment, the characteristics of this biopolymer must be improved. The characteristics of cellulose can frequently be modified to fit specific demands by utilizing appropriate chemical alteration in conjunction with appropriate mechanical treatments.

Adsorption, on the other hand, is a quick, simple, and cost-effective approach for treatment of wastewater with lower concentration of pollutants [8]. Activated carbon is a popular adsorbent at the moment, but its production costs are high, with higher regeneration conditions under harsh conditions [8]. Natural biopolymer are slowly gaining popularity due to their low cost, repeatability, and high efficiency of adsorption [9]. Among the biopolymers, cellulose has the higher isolation yield (1011–1012 t/y), being nontoxic, and having a high amount of hydroxyl groups, which are amenable for extended modification [8]. Examples include heavy metal removal employing cellulose-fabricated adsorbents and membranes for the purification of water [10]. A Physical and chemical approach, including chemical precipitation, membrane microfiltration, evaporation, adsorption, flocculation, and chemical oxidation, can be used to remove pollutants from effluent from the oil industry. All of the aforementioned techniques are expensive with high-energy consumption. Thus, using cellulose-based WW treatment methods are regarded as an alternative energy efficient and low-cost method. Therefore, this review focused on the effective utilization of cellulose derivatives (CD), including cellulose nanocrystals (CNCs), cellulose nano-fibrils (CNFs), cellulose nanoparticles (CNPs), and bacterial nano-cellulose (BNC) for the wastewater treatment. Moreover, we examined diverse cellulose processing methodologies to derive the CD for WW treatment. Additionally, the review highlighted the incorporation of these derivatives to other polymers/nanoparticles, with improving their performance on WW treatment is discussed.

2. Synthesis and characterization of cellulose and its derivatives for wastewater treatment

Anselme Payen, a French scientist, originally extracted cellulose from plants in 1839; since then, it has been the subject of several variations [10]. The global production of cellulose is around 1000 tons per year and is derived from plants, bacteria, wood, algae, and tunicates [10]. People then began extracting cellulose from bacteria, algae, and tunicates, and systematic research on extraction techniques increased [11]. A long-chain linear polysaccharide called cellulose is composed of repeated units of D-glucopyranose with β-1,4 glycosidic linkages [12]. The degree of polymerization (DP) is around 10,000 for cellulose chains, which is are found in nature, and 15,000 for native cellulose cotton [13]. Because of the larger number of hydrogen bonds connecting to the cellulose chain, not even water can dissolve it. Additionally, unaltered cellulose has weak mechanical and adsorption properties [14]. However, the polar groups are attached to the cellulose, which simplifies physical and chemical modification. By using the right modification methods, the application potential of cellulose can be enhanced [15]. The method that is most frequently employed by researchers is primarily done by using the hydroxyl groups that are attached to the cellulose chain during chemical modification. The main component of this hydroxyl functional alteration is an oxidation process [16], etherification reaction [17], esterification reaction [18] grafting copolymerization reaction [19]. By removing the macroscopic flaws in natural cellulose, nano-cellulose has superior mechanical characteristics over natural cellulose. The high cellulose Young's modulus (up to 114 GPa) is one of its desirable physical characteristics [20] for a single fibril with higher crystallinity (89 %) [21], higher polymerization degree (14,400) [22], and higher specific surface area (482 m^2g^{-1}) [23]. Two steps are necessary to separate cellulose from the cellulose source materials: (I) pre-treatment of raw materials to improve the uniformity of subsequent treatment processes; and (II) mechanical, acid, and enzyme hydrolysis is followed to separate the pre-treated raw biomass into crystals and microfibers. However, the price of bacterial cellulose is quite high [24].

The cellulose obtained from plants source is preferred for bulk production due to cost issues. Cellulose components can be found in wood, stalks, straws, grasses, plant fiber, stems, and shells [25]. Applications for cellulose can be considerably expanded by functionalizing it with hydroxyl groups [26]. The effects are added in converting the biomass for commercial use with modified physical and chemical properties. In general, there are two broad categories that can be used to categorize cellulose surface functionalization techniques: (I) Chemical alteration, including polymer grafting and 2, 2, 6, 6-tetramethylpiperidine 1-oxyl (TEMPO) oxidation; (II) Physical adsorption, including surfactant electrostatic surface adsorption; etc. In addition to the original cellulose fiber, mechanical means including homogenization and grinding can be used to create micro-fibrillated cellulose (MFC), which has a diameter of 10–100 nm and a length of 0.5–10 mm, or nano-fibrillated cellulose

(NFC), which has a diameter of 4–20 nm and a length of 500–2000 nm [27]. High pressure is used to crush cellulose fiber into smaller fiber during the homogenizing or grinding process. Amorphous and crystalline areas are seen in the derived MFC or NFC. The mechanical treatment consumes a lot of energy [28]; hence, the pre-treatment methods, including enzymatic [29], TEMPO-mediated oxidation [30], acetylation, and carboxymethylation [31,32] are followed to disintegrate the cellulose fiber. Different CNC morphologies are obtained, which depend, on the source of origin and applied hydrolysis conditions. Strong acids like sulphuric acid or hydrochloric acid are employed to dissolve the amorphous regions, producing extremely crystalline CNPs as a result. The width can arrange from a few nanometres to 50 nm, and the length ranges from 100 nm to 1000 nm [33].

Bacterial cellulose (BC) or bio-cellulose, which is produced as a direct by-product of the metabolism of various bacteria [34]. As a viable and appealing replacement for synthetically derived membranes, BC aims to create new bio-filters that are suited for wastewater treatment. These filters are environmentally safe and bio-based. Because BC membranes are produced using sugar fermentation methods, they are consistent with the goals of a bio-based economy in which chemicals are produced utilizing renewable sources of carbon [35]. Hussain et al. [36] recently reviewed BC productions, which can be expanded using agro-industrial waste as the substrate materials. The most popular bacterium for BC synthesis is *Gluconaceto bacterxylinus*, with a production capacity of 200,000 glucose molecules per second [37]. In comparison to plant cellulose, the biopolymer contains glucose monomers that are linked together by glycosidic β-1,4 bonds and arranged in three dimensions as nano-fibrils (thicker by 6–10 nm and wider by 30–50 nm), where hydrogen bonds are arranged in the inter- and intermolecular regions, providing excellent resistance to thermal treatment and adding mechanical properties with higher tensile strength [35]. Additionally, it has a remarkable capacity to absorb up to 100 times its weight in water and is biodegradable, non-toxic, and hypoallergenic [38].Due to the large number of surface hydroxyl groups, BC is easily modified chemically, broadening its range of potential uses. The literature reports a wide range of BC pore sizes, including the following: (N_2 adsorption technique, Brunauer–Emmett–Teller (BET) 45–800 nm [39], 12–24 nm (BET) [40]; 240–430 nm (scanning electron microscopy, SEM) [41]; and 10–20 μm (SEM) [42]. According to Li et al. [41], the resulting pore size depends on the experimental conditions, and even a single membrane will exhibit different pore sizes when seen from its lower and top sides using an electron microscope. The hole diameters make it easy to retain microorganisms, including *Escherichia coli*, *Shigella* sp., *Salmonella* sp., *Pseudomonas*, and *Enterobacter*, that are frequently found in water [41].

2.1. Cellulose derivatives (CD)

2.1.1. Cellulose ester

Although cellulose acetate (CA) is frequently employed because of its effective filtering, its characteristics must be modified for application, particularly in challenging conditions like high temperatures, organic solvents, and corrosive environments. The dense skin layer and minimally porous sub-layer of the CA membrane result in an exceedingly low flux. Additionally, there is a significant fouling issue with CA-based ultra-filtration membranes during filtration. Other polymers were blended for the formation of reactive functional groups, and efforts were made to improve its water permeability, membrane surface hydrophilicity, thermal stability, mechanical characteristics and resistance of fouling [43].

The most significant cellulose ester is CA. Commercial CA substitutes acetyl groups for OH groups in cellulose, with a degree of replacement of about 2.5. Cellulose triacetate (CTA) is the name of the derivative in which all of the cellulose hydroxyl groups have been substituted by acetyl groups. Following acetylation, partial hydrolysis up to DS 2.4–2.5 results in the production of commercial cellulose diacetate, generally known as acetate [44]. Numerous organic solvents, such as acetone, dimethyl formamide, dimethyl acetamide, chloroform, etc., readily dissolve CA. As a result, using it to spin fibres from liquids is quite effective. Strong-melting hydrophobic polymers CTA and CA both have strong UV stability, low flammability, and film transparency [45]. Acetates are CD that melt, but the temperatures needed to melt them cause partial deterioration; as a result, melt spinning is not employed to create CTA and CA fiber. Commercial CA fiber are spun using the traditional dry-spinning method, which involves a 4–6 m long heating column and a spinning dope comprised of acetone with a 25 % CA solution. On the other hand, although CTA is more frequently used to create films than fiber, it is typically spun using a methylene chloride or methanol solvent [45], because it enables the creation of low-flammability, very dimensionally stable films. It is not unexpected that CA is the most popular precursor for producing cellulose-based nanofibers (NFs), given its outstanding characteristics. Typically, wet spinning, electro spinning, solution blow spinning, and rotary jet spinning are used to create CA-NFs.

2.1.2. Cellulose ethers

The cellulose ether is used to manufacture NFs for a variety of uses. An important derivatization route that produces a huge class of derivatives with numerous potential uses is the etherification of cellulose [44]. Ethyl-cellulose (EC) is one of numerous ethers that are widely utilized in the creation of NFs [46,47], hydroxypropyl cellulose (HPC) [48], hydroxyethyl cellulose (HEC) [49], methyl cellulose (MC) [50], and CMC [51]. The degree of substitution (DS) has a significant impact on the solubility of cellulose ethers. Generally, alkyl-celluloses have additional hydroxyl groups replaced by alkyl groups, primarily methyl and ethyl. With alkyl chain length and DS, alkyl cellulose becomes more hydrophobic. The hydrophobic behaviour of a nano-fibrous membrane made of gelatin and ethyl-cellulose, for instance, has been demonstrated to increase with the amount of ethyl-cellulose in the composite [52]. With a DS above 2, commercial ethyl cellulose is thermoplastic, hydrophobic, and capable of extrusion to produce the films. Both methyl and ethyl celluloses are easily soluble in organic solvents, including ethanol, acetone, and toluene when their DS is over 2, however when their DS is lower than 2, these cellulose ethers improve their solubility in water. The commercial level, CMC is most used cellulose ether. Commercially produced CMC has a DS <1 (between 0.3 and 0.9), which is considered non-toxic, biodegradable, and suitable for use as food additives. The majority of commercial HPC has DS values of 1.5 to 3, which correspond to molecular substitution (MS) values of 0.8 to 1.2. A DS of 1 typically suggests HPC that is water-soluble. HPC, in contrast, is more hydrophobic than HEC. A mixture of polar solvents like methanol and water frequently makes a HEC a higher-soluble substance when compared to the MS value. Furthermore, it is established that HPC requires an MS of 4 in order to dissolve in cold water.

In the case of cellulose ether, electro spinning and coaxial electro spinning techniques are primarily used for spinning. Due to the difficulty in obtaining smooth electrospun HEC or HPC fibres, HEC is combined with polyvinyl alcohol (PVA) [49,53] to produce fibres of submicron size. Furthermore, crosslinking with glutaraldehyde is typically done post-spinning because the generated substance is water-soluble [49] or photo-chemically produced during electro-spinning [49]. Besides PVA, polyacrylonitrile (PAN) alongside HEC is used in the production of NFs with a diameter of 100–300 nm [54]. Additionally, ethyl cellulose is used after spinning with polyvinyl pyrrolidone (PVP) [55]. According to Yu et al. [56], coaxial electro spinning was utilized, with EC serving as the core polymer and PVP serving as the sheath polymer.

2.2. Synthesis of BNC

Carbon sources with lower molecular weights like D-glucose, are used to create BNC by the use of a biotechnical assembly method, whereas CNF and CNC are derived from sources of plant-based cellulose [57]. There are two main mechanisms associated with the multistep process of

BC synthesis: firstly, uridine diphosphoglucose (UDPGIc) production, and then, cellulose synthase polymerizes glucose into long, unbranched chains (the β-1 → 4 glucan chain). Depending on the carbon source that is available, carbon molecules such as dicarboxylic acids, pyruvate, glycerol, hexoses, and dihydroxyacetone can enter the gluconeogenesis and pentose phosphate cycles to begin the creation of UDPGIc. Bacteria are grown in standard aqueous nutritional media, and BNC is extracted as an exopolysaccharide at the air interface. This produces a thick gel made up of 99 % water and three-dimensionally interwoven bacterial cellulose nano-fiber (pellicle). The topology of the BNC nano-fiber network is controlled by factors such as strain type, post-drying procedures, culture media additions, cultivation type, and growth condition [58]. The BNC was made up of nano-fibrils with a width (2–4 nm), and formed into a ribbon-shaped fibril with a length of about 100 um and a width of around 100 nm [59]. In BNC, cellulose is pure and free of lignin and other extraneous materials, with functional groups like carbonyl and carboxyl often missing. BNC showed an extremely long polymer chain (up to 8000) with up to 90 % polymerization and crystallinity [60]. BNC is the purest form of cellulose, which has an entangled structure. It can be transformed into carbon compounds or integrated with conductive materials to store energy in a flexible manner [61]. Two methods are involved in the synthesis of BNC using microbes: agitated culture and static culture. Static culture is produced when a leather-like white pellicle of BC is formed at interface of air and liquid. In stirred culture, BC is prepared and distributed throughout the culture medium, producing uneven pellets or suspended fiber. Because two distinct processes show varied morphologies and mechanical and physical properties of the synthesized polymer, the choice of production method relies on the final attributes needed for applications. For instance, cellulose made by stirring culture is not as mechanically strong as cellulose made by static culture. Stirred cultures also yield less than static cultures and have a higher chance of causing mutations in the microbe, which could have an impact on BNC production. However, static culture necessitates a longer culture period and a larger cultivation area [62].

3. Modification of cellulose

These cellulosic materials are transformed into CNCs, CNFs, CNPs, and BNC, which is naturally obtained for wastewater treatment, through the application of chemical or mechanical pre-treatments. Cellulose is chemically modified with the process of esterification, grafting modification, etherification, oxidation and cross-linking to obtain the CD. Similarly, acid, alkali and organic/inorganic treatment are performed to obtain the CD. Nano-cellulose is typically divided into four groups based on its origin: MFC, CNC, CNF, and BNC [63]. Further modifications are made to these nano-cellulose including (CNCs, CNPs, CNFs, and BNCs) to create membrane filters.

3.1. Chemical modification

3.1.1. Esterification

Cellulose ester is the result of the esterification reaction occurred between the hydroxyl group of cellulose (present at molecular chain) and acid anhydride, acid, or acyl halide, which occurs under acid catalysis conditions [64]. The studies revealed that heterogeneous systems is not efficient in controlling the reaction process, which was detrimental to cellulose esterification and had a lower DS; however, homogeneous systems could enhanced cellulose esterification reaction speed and reduce cellulose disaggregation of the main chain [65]. For further improvement of cellulose esters, a homogenous esterification system is required. Lithium chloride (LiCl)/*N*,*N*-dimethyl acetamide (DMAc), and ionic liquid (IL) are cellulose solvents with higher thermal stability and reusability [66]. Meanwhile, cellulose breakdown in a homogenous system promotes the introduction of functional groups, which broadens the applicability of cellulose esters. Additionally, Willberg-Keyriläinen et al. [67] generated a series of cellulose esters, cellulose was dissolved in a 5 % LiCl/DMAc solution, and then fatty acid chlorides with varying side chain lengths (C6-C18) were incorporated in the solution of cellulose. After that, CNF film was used for coating the cellulose esters to create a three-layer film of ester-CNF-ester. The three-layer films have a flat surface, excellent mechanical qualities, and act as a water vapour barrier. It was potentially used for food packaging and electronic printing due to the superior qualities of membrane materials. Similarly, Zhang et al. [68] employed bleached hardwood cellulose as the raw material, 1-butyl-3-methylimidazolium chloride, IL as the reaction substrate, and interacted with -caprolactone monomer to produce cellulose-polycaprolactone graft copolymer under homogeneous circumstances. The maximal graft ratio of the poly-caprolactone graft copolymer is 86.7 %.

3.1.2. Grafting modification

The active hydroxyl groups of cellulose serve as a grafting location in cellulose graft copolymerization. Under the condition that the advantages of cellulose materials are not totally destroyed, the polymer chain generated by the monomer's polymerization reaction is grafted onto the main chain of cellulose via covalent link, providing cellulose additional features. Graft copolymerization is commonly accomplished using atom transfer free radical polymerization, free radical polymerization, ionic polymerization and ring-opening polymerization. And it is typically done in three ways: “grafting through”, “grafting to”, and “grafting from”. “Grafting from” is the most widely utilized approach. This approach is easier to manufacture cellulose graft copolymers with high graft ratios due to involvement of smaller monomer molecules and the low steric resistance [69]. According to Abdelwahab et al. [70] by atomic radical polymerization, they successfully grafted acrylic acid (AA) and acrylamide (AM) onto CA matrix, and evaluated the lead ions absorption from wastewater by CA and by modified CA. The modified CA significantly improved the adsorption of Pb (II) ions, adsorbing 66.67 mg/g. Additionally, Jiang et al. [71] initially created a new cellulose-based polymer chain transfer agent (Cell-CTA) with cellulose 2-bromoisobutyrylate and 1-dodecanethiol as materials ingredients, and then grafted n-butyl acrylate (BA) and AM onto Cell-CTA by reversible addition-fragmentation chain transfer polymerization to create a cellulose graft copolymer with excellent mechanical attributes.

3.1.3. Etherification

Cellulose ether is derivative of cellulose generated under specific conditions by the interaction of alkaline cellulose with an etherifying agent. The ether groups are partially or completely replaced by hydroxyl groups on cellulose macromolecules. With the advancement of research on cellulose ether, it has emerged with high performance with better reaction systems. Additionally, Nagel et al. [72] in a homogenous phase, methylcellulose (MC) was produced utilizing a LiOH/urea reaction medium and dimethyl sulphate as an etherifying agent. The etherifying agent was dipped gradually at 0 °C, then raised it to 22 °C and agitated it for 24 h. Isopropanol was used to wash the precipitated product. The product's DS was 1.07–1.59. Similarly, Li et al. [73] used LiOH/urea aqueous solution, a series of cyanoethyl celluloses with varying DS were synthesized using acrylonitrile (AN) as an etherifying agent. CEC had the highest DS of 1.81. CEC with DS values range from 0.470 to 1.010 are water soluble, and those with DS values >1.120 may show their higher solubility in organic solvent. Dong et al. [74] used the one pot techniques to synthesized ethyl pent-4-enyl cellulose with a combination of sodium hydride and ethyl iodide, and several types of amorphous solid dispersed amphiphilic cellulose ethers which were obtained via an olefin cross-metathesis reaction with ethyl pent-4-enyl cellulose and AA or acrylate monomer as raw material.

3.1.4. Oxidation

There are two types of cellulose oxidation: selective oxidation and non-selective oxidation. Sodium hypochlorite, hydrogen peroxide, and persulfuric acid are examples of non-selective oxidants. To create CD

with specified structures, selective oxidants can be instructed to breakdown the cellulose's hydroxyl groups [75]. Wen et al. [76] used to deoxidize cellulose, an eco-friendly oxidation technique combining UV light, hydrogen peroxide, and ozone was employed. The oxidized cellulose was then homogenized using high pressure to form CNFs. The usual length and breadth of CNFs generated using this sustainable process can reach 11 m and 22 nm, respectively, indicating that the derived high-quality CNFs have a wide range of applications.

3.1.5. Cross linking

The application of crosslinking compound (including epichlorohydrin & *N*,*N*′-methylene bis-acrylamide) to link cellulose or CD to various polymers to generate three-dimensional network structure products, which can be use as the materials for the WW treatment.

3.2. Organic/inorganic treatment

To boost adsorption capability, chelation is performed to mercerized and non-mercerized cellulose using EDTA dianhydride [77]. Cotton pellet-derived lignocellulose is used to eradicate arsenic contamination from aqueous regions. Prior to the process, cotton pellets are treated with ferric chloride. The adsorbent was regenerated for 5 times before its adsorption capacity diminishes by approximately 11.5 % [78]. After alteration, waste materials having a high cellulosic component can be employed for adsorption of heavy metals. Similarly, Jamshaid et al. [79] reported a study employing mercerized cellulose was described. Cellulose was mercerized with NaOH, then washed with distilled water and acetone, dried, and stored. Cellulose was then allowed to react with succinic anhydride in the presence of pyridine. For Cu^{2+}, Cd^{2+}, and Pb^{2+}, the concentration of adsorbed heavy metals were 30.4, 86, and 205.9 mg/g, respectively. Gurgel et al. [80] proceeded with their investigation by altering the previously studied mercerized cellulose with triethylenetetramine to see whether there was any chance of improvement in the rate of adsorption. However, the study discovered that modifying cellulose with triethylenetetramine actually reduced its capacity for adsorption. In another modification attempt, Hokkanen et al. [81] employed the carbonated hydroxyapatite (CHA) to create CHA-modified micro-fibrillated cellulose for Cd^{2+} and Ni^{2+} adsorption. The experiment yielded favourable results.

3.3. Alkali treatment

To remove arsenate and from aqueous solutions, iron oxyhydroxide is used for treatment to produce the cellulose beads. It was replenished for up to four adsorption cycles [79]. Similarly, Shukla and Pai [77] contributed to this effort by employing jute fibres to remove Ni(II), Cu (II) and Zn(II) from aqueous solutions. Agricultural wastes are generally rich source of biopolymers with functional groups which has the greater potential for pollutants adsorption from WW. The functional groups in biomaterials can also be chemically changed to boost adsorption rates. The hydroxyl group is one such significant functional group. Jute fibres (58–63 %) and lignin (12–14 %) are abundant in this study. They were altered to create two new forms. The first is created through dye loading, whereas the second is created through oxidation using sodium hydroxide. These two kinds of jute fibres were more effective than the unmodified form. The pH of the system effected over efficiency of adsorption. The adsorption capacity decreased as the pH decreased. Only during regeneration with caustic soda, the capacity for the adsorption in the jute fiber was sustained during adsorption/desorption process.

3.4. Acid treatment

The Cu, Cr, and Ni were absorbed using oak sawdust [82]. The procedure includes hydrochloric acid preparation of oak sawdust. Sawdust is a readily available lignocellulosic material that is ideal for wastewater adsorptive treatment. Meena et al. [83] also utilized *Acacia Arabica* sawdust to adsorbed Cr (VI), Cu (II), Hg (II), Pb (II) and Hg (II). Çavuş et al. [84] reported for the adsorption of Cu^{2+}, Pb^{2+} and Cd^{2+} where, HEC was grafted with AA with incorporation of poly (ethylene glycol) diacrylate as cross-linking agents.

3.5. Synthesis of CNCs

In order to form well-defined crystalline domains, amorphous cellulose fibres are hydrolyzed with acid as part of the CNC preparation technique. Amorphous cellulose is efficiently broken down into the solution by acid hydrolysis, which also removes CNC [85]. This led to the formation of crystalline structures known as CNC [86] as shown in Fig. 1. These environmentally friendly nanoparticles feature a very large specific surface area, strong mechanical support, excellent functioning, and a surface that is highly biocompatible. They are heavier than steel and more compact than aluminium. With their dependence on the source, they also have a significant aspect ratio (length/diameter), ranging from 30 to 150 μ [87].

3.6. Synthesis of CNFs

Through mechanical, chemical, and biological isolation techniques, the CNFs are removed. CNFs are produced mechanically using a variety of physical techniques, including ultrasonication, micro-fluidization, high-pressure homogenization, and grinding and crushing [89]. Moreover, CNFs can also be created through chemical processes such as solvent extraction, oxidation, and acid hydrolysis. However, deploying this method of nano-cellulose production degrades the end product and the quality of the fibres (lower fibres diameters) [90]. In addition to chemical and mechanical techniques, biological therapy can also be used to extract CNFs. Furthermore, the ability to naturally obtain BNC fibrils on a nanoscale makes them intriguing [91].

3.6.1. Mechanical methods for synthesis of CNFs

The homogenization method is mostly used in the mechanical process to break down cellulosic fibres and separate the nano-fibrils from them. Cellulose nanofibers (CNFs) are made of nano-cellulose that has been refined, homogenized, and ground via a mechanical defibrillation process. A study applied these techniques to produce CNFs from softwood pulp by ball milling it at room temperature and with ambient pressure [92].

3.6.2. Chemical methods for synthesis of CNFs

By hydrolyzing the amorphous portions of the CNFs, the crystalline portion can be extracted chemically. The hydrolysis process included light mechanical treatment after acid hydrolysis and TEMPO-interceded micro-fibril surface oxidation. Consequently, the delayed disruption of inter- and intermolecular hydrogen bonds increases the accessibility and reactivity of the cellulose structure while reducing its crystallinity. Therefore, chemical techniques including hydrolysis by acid, pre-treatment using acid and alkaline, and pre-treatment via oxidation can reduce power consumption, improve the disintegration process, and boost the yields of nano-fibrils and cellulose [93]. The hydrolysis of wood cellulose fibres was the basic chemical treatment process. These fibres are made up of a combination of crystalline and amorphous areas called micro-fibrils. The further separation of micro-fibrils into CNFs is caused by the amorphous regions, which serve as material structural flaws. High-crystallinity fibres are produced by isolating the CNF through acid hydrolysis, which also eliminates the amorphous units of the cellulose's original structures. It is also possible to create CNFs with a chemical hydrolysis process by using mineral acids likeH_3PO_4, H_2SO_4, and HCl [94]. 1–10 % NaOH at moderate temperatures can be used for alkaline-based hydrolysis. However, in order to conform to the nano-cellulose structures, cellulose was additionally dissolved in trifluoroacetic acid, DMSO, *N*-methyl morpholine-N-oxide (NMMO), and DMF

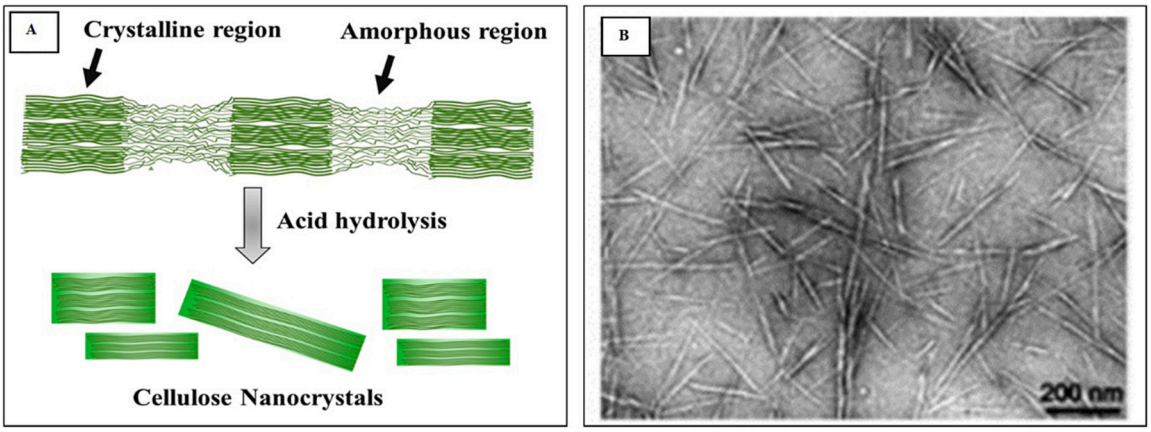

Fig. 1. Isolation of cellulose nanocrystals by acid hydrolysis (A) and its microstructure (B). Panels (A and B) are reproduced with permission (copyright © 2021 Elsevier Ltd., Amsterdam, the Netherlands) from Sayyed et al. [88].

[95]. Because they offer the benefit of allowing for the further usage of lignin and hemicelluloses in addition to the primary product of cellulose, organic solvents have also been used in the production of nano-celluloses more recently.

3.6.3. Biological methods for synthesis of CNFs

Biological techniques refer to the process of extracting crystalline fibres from cellulose micro-fibrils using biological means, such as enzyme-assisted hydrolysis, followed by mild mechanical therapy, or a combination of these methods [93,96]. Hydrolysis using enzymes is a useful technique that uses mono-component endoglucanase to precisely hydrolyze the glycosidic linkages along the cellulose chain, simplifying defibrillation [97,98]. To enable the hydrolysis agent to penetrate the enzymatic pre-treatment, several steps have been necessary. The hydrolysis results in the separation of cellulose, hemicellulose, and lignin which reduce the DP while improving the porosity of particles through substratum layers. Accordingly, the bacterial cellulose nano-fibres production technique is a green development method that does not involve the use of hazardous chemicals [99].

3.6.4. Spinning methods for synthesis of CNFs

The process of spinning polymeric fibres involves a number of processes that are generally dependent on the features of the polymer being spun, such as its solubility, thermal behaviour, and whether it can be melted without degrading the polymer. Electrospinning is commonly described approach where electrical field is generated at higher voltage between the conductive collector and nozzle, resulting of polymeric jet for uniaxial elongation from a molten ink, solution, and emulsion form. To manufacture filaments, continuous threads of limitless length, various spinning techniques can be used. Wet spinning, dry spinning and dry-jet wet spinning methods are three common methods of solutions spinning [100]. A spinning dope is created in any spinning method by melting or mixing the precursor of polymer, which is then extruded via a spinneret. Evaporation of solvent from heating environment and cooling process are to solidify the dope. Since cellulose does not melt, it is essential to dissolve it in the right solvent. Especially attention is given on the solvent used to prepare spinning dopes since the characteristics of the associated solution considerably influence the spinning processes and processing requirements. Several methods are utilized to spin CNFs, with solution blow spinning, wet spinning, dry spinning, electro-spinning, and hybrid dry-jet wet spinning, being the most often employed methods (Table 1).

3.6.4.1. Electrospinning. The most well-known and often used method for creating NFs is electro-spinning. The following are some conditions of the solvent that must be met for electro-spinning NFs from polymer solutions to be successful [105], the following: (I) semi-conductivity with moderate charge capacity; (II) high volatility to aid in the solidification of polymer fibres; and (III) capacity to dissolve the polysaccharides with minimal intermolecular interactions. The structural complexity of cellulose and its solubility issues restricted its application to generate CNFs utilizing electrospinning. But in 2005, author reported using electrospinning to successfully create pure CNFs [106,107] from solution of cellulose using NMMO. Kulpinski, for instance, investigated how to best use dry-wet electrospinning to produce CNFs [45]. After being mercerized with NaOH, the cellulose from the spruce pulp was then dissolved in a commercial 50 % NMMO solution. Between 1 and 4 wt% of cellulose was present in NMMO. Because the cellulose's NMMO solvent crystallizes when it cools [45], electro-spinning was performed using heated spinning dope at temperatures ranging from 80 to 100 °C. During spinning, the collector was immersed in a coagulation bath comprising water or water containing surfactants at a working distance

Table 1
Overview of the most popular spinning processes, precursors, and solvents for developing cellulose nanofibers[a].

Solvents	Spinning method	Spinning precursor	Applications	Reference
LiOH/NaOH/H_2O/Urea, aqueous dispersions	Wet (spinning)	CNFs and cotton pulp	High-strength cellulose for the manufacture of textile materials	[101]
NMMO, LiCl/DMAc, TEA, DMF, Dichloroethane	Electro-spinning	Hardwood and softwood pulp, CNCs, cotton	Biomedical uses, delivery of medicine, wound dressing, UV protection, and scaffolding	[45]
1-Allyl-3-methylimidazolium	Dry-jet wet (spinning)	CNFs and pulp	Fiber that are strong and stable in the heat	[102]
Water	Dry (spinning)	CNFs isolated from various sources	Filaments with high mechanical strength for use as reinforcements in a variety of composite materials	[103]
1-Ethyl-3-methylimidazolium acetate, 1-ethyl-3-methyl-imidazolium diethyl phosphate, LiCl/DMAc	Solution blow (spinning)	Pulp	Nonwovens with high tensile strength	[104]

[a] CNF: Cellulose nanofiber, CNC: Cellulose nano-crystals, NMMO: *N*-methyl-morpholine-N-oxide, DMAc: Dimethylacetamide, LiCL: Lithium Chloride, LiOH: Lithium Hydroxide, DMF: Dimethylformamide, TEA: Triethanolamine.

of 10 to 15 cm from the spinning nozzle. According to Kulpinski [108], the concentration of cellulose needed to successfully spin fibres was 2 weight percent (wt%); a concentration of 1 wt% was insufficient to produce NFs. The applied voltage, on the other hand, was unable to trigger the production of a Taylor cone and, eventually, the NFs, because 4 wt% was too viscous to let the process to proceed properly. The average diameter of the fibres produced by the 2 wt% solution was <500 nm. It's interesting to note that surface motion allowed for the production of fibres when the coagulation bath surface was moving as opposed to being static [45].

He et al. (2015) studied over critical aspects of the electrospinning method, such as solution intrinsic properties, employing cotton cellulose and LiCl/DMAc [109]. The authors discovered that appropriate concentration of cellulose was required for electrospinning, because lower concentrations resulted in lowering of viscosities and prevented the continuous fibres formations in the collector, while high concentrations resulted with higher surface tension and viscosity, reducing the electrospinning process. Furthermore, a correlation was discovered between the supplied voltage and the fiber diameters diameter distribution. The radial force was stronger than polymer jets cohesive force at the elevated voltage.

Similarly, Kim et al. [110] investigated and contrasted two methods for preparing the solutions of cellulose using electrospinning process. The comparison was made between two solvents including LiCl/DMAc and NMMO, as well as the effect of air drying versus coagulation bath on fiber shape were studied. Several significant results were drawn in this analysis. Firstly, the fibres were produced uniformly after employing coagulation bath, which allows for more efficient solvent removal from fibres. The usage of LiCl/DMAc necessitated to heat the collector in order to extract dry fibres, and on these conditions the coagulation and nozzle were kept at ambient temperature. With the NMMO/water system, the cellulose solution required thermal processing at 70–110 °C before the spinning process, while the collector was retained at room temperature and the coagulation bath was cooled down to 9–10 °C. Both techniques produced fibres with sizes ranging from 250 to 750 nm. Furthermore, fibres formed from the LiCl/DMAc system were predominantly amorphous, but fibres derived from the NMMO/water system ranged from 40 to 60 % crystallinity depending on the electrospinning process parameters [110].The application of volatile and occasionally poisonous solvents represents an obstacle for cellulose fiber electrospinning. Because the world is shifting toward eco-friendly and green technologies, this should be handled in the future. Hell et al. [111] has presented an ecologically safe method for producing CNFs. Because cellulose in-soluble in water, it is oxidized to dialdehyde cellulose before electrospinning in conjunction with PVA utilizing water as the solvent reagents. Dialdehyde cellulose cannot be spun alone, but when combined with PVA, NFs with diameters ranging from 200 to 500 nm were generated.

3.6.4.2. Dry spinning. Dry spinning can be used to create strong filaments from isolated nano-fibrils by forcing them to be oriented [112]. In the work of Hooshmand et al. [113], first, by mechanically milling bleached banana rachis pulp, the authors extracted CNFs. Different resulting concentrations (8 %, 10 %, and 12 %) of spinning dope were produced by gel concentration employing various centrifugation steps after the first step, which involved converting a 2 wt% solution to hydrogel. A capillary rheometer was loaded with spinning dope at the required concentration, and filaments were spun manually at various spinning rates and collected on a glass plate. With a rising spinning rate and a declining CNF concentration in a spinning solution, the mechanical characteristics of the filaments that were formed demonstrated an increasing value. Furthermore, the scientist's noted that the uses of biomass waste to generate the CNF filaments using a straightforward process have significant economic potential and that they exhibit mechanical qualities comparable to the viscose filaments (11 GPa). Later Hooshmand et al., [114] used hydroxyethyl cellulose (HEC) to help spin cellulose filaments using a capillary rheometer and dry spinning. As a result of the HEC, the dope's wet strength rose, enabling stable spinning at low CNF concentrations. HEC and cold drawing post-spinning were also added, which enhanced the CNF orientation in the filament and increased the modulus and tensile strength by 70 % while lowering hydrophilicity. The author investigates the feasibility of dry-spinning dimethylformamide solutions to make CNC and polylactic acid composite fibres [115]. The addition of 1 % CNC maximized the crystallinity, an increase of around 30 % for the dry-spun composite fibres.

3.6.4.3. Wet spinning. In wet spinning, which works oppositely to dry spinning, spun filaments coagulate in a bath to create fiber before drying. It is the most popular method for cellulose fiber preparation. Typically, the spinneret is submerged in the coagulation solution, and fibres are generated as soon as it opens. For the wet spinning, the non-volatile solvent is used and for the removal of solvent the coagulation bath is operated. According to Zhu et al. [116],the cotton pulp was used to create wet-spun NFs with a diameter of 25 nm. The LiOH, urea, NaOH and water were used to dissolve the cotton pulp to produce spinning dope with a 5.8 wt% concentration. At a temperature of 5 °C, the coagulation bath comprised solution of 5 wt% sodium sulphate aqueous and 15 wt% phytic acids. With fiber strengths of 3.5 cN/dtex for the dry state and 2.5 cN/dtex for the wet state, respectively, the resulting multifilament material demonstrated good mechanical capabilities.

3.6.4.4. Hybrid dry-jet wet spinning. Wet spinning is essentially the same technology as dry-jet wet spinning, with the addition of an air gap between coagulation bath and the spinneret [117]. Dry jet wet spinning was applied by Song et al. [118] to create bio-nanocomponents fiber by combining nano SiO_2 with microcrystalline cellulose (MCC). The ionic liquid 1-allyl-3-methylimidazolium chloride (AMIMCl) served as the microcrystalline cellulose's solvent. The diameter of the silica particles was 80 nm. Various ratios of nano-SiO_2 (0.2–0.6 %) were added to 5 wt % MCC solutions for spinning. The coagulation bath included de-ionized water, and the air gap measured 3 cm. The spinning fibres were then dried under vacuum for 48 h. The authors noted improved SiO_2 dispersion in cellulose fiber and an improvement in the composite fiber's thermal stability. Superbase-based ionic liquid(ILs) have showed outstanding cellulose dissolving capacity, and high-tenacity regenerated textile fibres was produced using the dry-jet wet spinning techniques [119].

3.6.4.5. Solution blow spinning. Medeiros et al. (2009) proposed SBS as good alternative to electrospinning methods. The fundamental benefits of SBS over electrospinning, is due to higher rate in production of NFs and films with identical qualities to those formed by electrospinning, which allows for the use of virtually any type of solvent [120]. The manufacture of CNFs from wood pulp is done by the solution blast spinning technique [121]. In an SBS device, fiber travels from the nozzle to the collector along with thermal treatment in a 2 wt% cellulose solution in 8 % LiCl/DMAc. However, the authors emphasized that rather than heating air at ambient temperature, the spinning cabinet region from the collector to the nozzle was heated. As a result, a temperature gradient was evolved, which resulted in an uncontrolled temperature along the spinning line region. In other words, it was unclear what the temperature was exactly during the spinning. Based on the temperature that was measured close to the collector, or the end of the spin line, the authors provided an estimated spinning temperature [121]. The produced NFs have 260–1900 nm as their average diameter. Several years later, Jedvert et al. [122] utilized blow spinning with a dry-wet solution. A wide variety of concentrations of pulp of dissolved cellulose in the ionic liquid 1-ethyl-3-methylimidazolium acetate (EMIMAc) were spun into fiber, and the fibres were gathered on a rotating cylinder dipped in water. The solution of cellulose was heated at a specific temperature

(between 65 and 95 °C) before SBS. The resultant fibres have a diameter in the range of 2 to 20 μm.

4. Cellulose based nano-composites for wastewater treatment

Applications of nanoparticles and nanocomposites (NC) for wastewater treatment are reported in some of the current evaluations [123–126] or of cellulose-derived materials in the treatment of WW [127]. Researchers are concentrating on cellulose or inorganic nanoparticles composite materials due to their special qualities and functions [128]. Because cellulose has more hydroxyl groups with a hydrophilic nature on the surface, it has several fascinating qualities, including higher thermal, mechanical, and biodegradability, higher surface properties, ease of availability, and facile function [129]. Because of these qualities, cellulose and materials derived from cellulose are very beneficial when used as a platform for cleaning water [130]. The cellulose/NPs prevent agglomeration, ensure colloidal security, and facilitate the simple separation of magnetic components following treatment. For their pilot-scale applications, membrane technology has been investigated as a means of overcoming several important obstacles, including limited mechanical strength, fouling, and delayed purification [131]. Modifying the membrane surface prevents them from creating strong material [132]. When the appropriate materials are incorporated to functionalize membranes, fouling may be avoided, and their permeability, mechanical stability, and heat tolerance are increased [10]. Additionally, adding NC to the polymer matrix could enhance its mechanical qualities [133]. Both inorganic nanoparticles and cellulose are thought to be good water-decontaminating materials when combined, but the combination exhibits far greater innovation and promise [134]. The cheap cost, biodegradability, and exact strength of cellulose—both chemically and mechanically—along with its abundance of hydroxyl functional groups, which cover a large surface area and promote electrostatic interaction or hydrogen bonding, allow for the elimination of numerous harmful contaminants. Through physical and chemical contact, the surface of cellulose is functionalized or grafted with appropriate molecules to provide even improved purification efficiency in the separation of harmful contaminants. Therefore, due to their enormous surface area, catalytic, adsorption, and possible antibacterial properties, NPs have also been identified as feasible decontaminants.

5. Cellulose-based sustainable materials for wastewater treatment

5.1. Cellulose-based adsorbents

A rapidly expanding field of study that offers a variety of enticing choices for wastewater treatment is biodegradable biomass as a raw material. For practical water treatment, its repeatability and degradability offer a viable option. Textile dyes, heavy metal ions, oil stains, and personal care items are just a few of the pollutants found in wastewater discharges that are hazardous to both environmental and human health [6]. Cellulose is naturally hydrophilic and is modified with hydrophobic or oleophilic ingredients to remove organic contaminants such oils and cyclohexenes [135]. The cellulose are modified with other biopolymers including chitosan, polymers, dendrimers, and nanomaterials like noble metallic nanoparticles, carbon, carbon nanotubes, graphene oxide, metal oxides, zeolites, and metal-organic complex [136,137], which added advantages in the WW treatment.

The strong dependency to pH mainly to strong base and strong acid it can be used as regeneration agent for adsorbents whose primary adsorption principles are followed by electrostatic contact. The adsorbents are used to remove the pollutants from the solutions. Strong acids like nitric acids, sulphuric acids, and hydrochloric acids, strong bases like potassium hydroxide, and sodium hydroxide, complexing agents like EDTA, and organic solvents, including ethanol, methanol, and acetone are all frequently employed as regeneration reagents [8]. The appropriate chelating agents for removing the contaminants are employed as regeneration agents in the adsorbents, whose adsorption mechanism is complexation. Organic solvents can also be used to rejuvenate adsorbents that absorb organic contaminants. If adsorbents are required to be employed in a real wastewater treatment system, their ability to be reused may be crucial. Hydrogen bonds, complexation, and electrostatic interactions are frequently part of the adsorption mechanism. The ability to eliminate these interactions is thus required of the chosen regeneration reagents. It has been extensively investigated how heavy metals are absorbed by biomass materials [138]. Ni^{2+}, Cd^{2+}, Pb^{2+}, Cu^{2+},$Fe^{3+}Co^{2+}$, and $Zn^{2+}$are examples of heavy metals with low-valent groups present in water [139]. In general, ion exchange, adsorption, and complexation on the adsorbent's surface and interior pores make up the adsorption mechanism. Due to its high degree of porosity, considerable specific surface area, and the presence of hydroxyl groups with a hydrophilic nature, cellulose is a potential substrate for heavy metal ion adsorption. For heavy metal ions with high valent group ions like Cr^{6+}, the dichromate might gradually hydrolyze and take the form of Cr^2 O_7^{2-} and CrO_4^{2-}[140].These ionic forms attach to biomaterials through ion exchange and electrostatic adsorption. The quick elimination of Cr^{6+} from aqueous regions is thought to be due to the synergistic impact of in situ reduction and electron donor coordination. $Cr^{6+}$are chelated by oxygen with their functional groups on the adsorbent surface by reducing to a simple cation. The solution pH will also alter the shape of the metal ions in the water at the same time. The REDOX processes, hydrolysis, metal ions polymerization, coordination, can all be impacted by pH changes. The presence of surface functional groups on the surface of the adsorbent's ionic state may be impacted. The biomaterials adsorption capacity drops significantly as the pH of the solution rises, demonstrating that electrostatic interaction dominates the adsorption process. The adsorption efficiency of the adsorbent might be impacted by its surface structure. In a report, macro-porous fiber beads were made using the template approach, and tentacle-shaped polyisohydroxamic acid was fixed to the fiber beads as adsorption ligands [141]. Large cellulose bead pores lower mass transfer resistance, which increases the rate at which heavy metal ions are transferred inside the adsorbent. Additionally, the pores may offer a readily available active site for polymer grafting, boosting the adsorption capacity. A permeable and amino-rich cellulose-based composite adsorbent (PEI-PCS) with anisotropic feature was developed by covalently cross-linking polyethyleneimine to delignified maize straw [142]. When combined with the porosity of the straw substrate and the binding ability of the amino group to metal ions, the -prepared PEI-PCS exhibited versatility (different metal ions), rapid adsorption behaviour (the achieved adsorption equilibrium was 180 min), a large capacity for adsorption (85.47 mg/g for Cu (II)), and good resilience (70 % effectiveness of adsorption after 5 cycles). The adsorption mechanism was additionally modelled with pseudo-2nd -order and the Langmuir isotherm.

Scientists have recently worked hard to produce ecologically safe cellulose-based adsorbents for the sorption of heavy metals. The fundamental issue is the lack of cellulose functional groups for the formation of complexes with heavy metals. As a result, the sorption qualities of cellulosic materials are insufficient. To address this issue, cellulose is typically changed using a variety of processes. It is critical to select a suitable approach for processing polysaccharide-based components when developing new sorbents with increased sorption characteristics for heavy metal ion extraction. Various writers have suggested numerous ways, including mechanical, physical, physicochemical, chemical, and biological approaches [143] to alter cellulose-based polymers, such as flax fibres [144].

Chemical modification is a viable strategy for changing cellulose-containing sorbents since it may be done with inexpensive and readily available reagents such as acids, bases, mineral, oxidants and organic compounds. They can all be used to alter cellulose-based polymers. The modification is performed to improve the presence of sorption-active groups with increasing the inner adsorption surface and develop new

sorption points, hence improving natural sorbents' sorption capacity [145]. Cellulose-based sorbents are made functional through esterification [146], etherification [147], sulfonation [148], and oxidation process [149]. It improves the quality and efficiency of the adsorbents. Researchers are becoming increasingly interested in cellulosic materials as adsorbents due to their highly effective adsorption of heavy metal ions [150]. In grafted form, these biopolymers can also be employed for heavy metal ion sorption [143]. The sorption isotherm of metals ions was investigated using chemically modified short flax fibres [151]. The alteration was carried out for the flax cellulose oxidation by sodium metaperiodate to generate dialdehyde cellulose. The results of equilibrium and kinetic analyses of the sorption of Cu (II), Cd (II), and Fe(II) ions from fluid solutions by primary and modified cellulose sorbents were presented in the article. SEM spectra show that the surface morphology of the changed sorbents differs from the original. The formation of amino- and sulfo groups in short flax fibres during the modification step is revealed by IR spectra.

The adsorbent regeneration as well as the adsorbate recovery is equally important during the adsorption of heavy metals and dye. The regeneration studies was conducted using different desorbing agents including HCL, HNO_3, H_20, NaOH, NH_3OH, HCL/thiourea, and HNO_3/thiourea [152]. The results concluded that adsorbent could be reused 5times at least without noticeable changes in adsorption capacity during repeated adsorption-desorption operations. The results concluded that cellulose adsorbent has excellent ability to reuse in Cr (VI) adsorption by using 2 M NaOH desorbing agent.

5.1.1. Adsorption mechanism

Electrostatic interactions, hydrogen bonds, ion exchange, complexation, van der Waals forces, and π-π interactions are the primary adsorption processes of nano-cellulose adsorbents to metal ions and dyes [99]. Van der Waals forces, π-π interactions, hydrogen bonds, and other non-electrostatic attractions are prevalent in the dye adsorption when compared with metal ions. The nature of interaction and intensity between adsorbent and adsorption sites are determined by the charges on the surface of adsorbent. The zero-charge point (PZC) is a critical characteristic that shows the pH value of adsorbent surface without providing the charge value (Melo et al., 2018). The cationic ions adsorption is suitable under the conditions (solution pH $>$ pH $_{PZC}$) for the adsorbent, similarly, for anionic molecules the adsorption is favoured under conditions (solution pH $<$ pH $_{PZC}$) for the adsorbent [153].

At a higher pH level, the carboxyl groups are capable of being deprotonated, allowing positively charged metal ions and anionic dyes to be adsorbed via electrostatic interactions. The carboxylated CNFs with a high carboxyl content had the maximum adsorption ability for Cu (II) and the cationic dye MB, according to the citric acid/hydrochloric acid hydrolysis technique [154]. The adsorbent's potential for MB improved as it raised pH in the range of 4–10. This conclusion could be due to the fact that the more deprotonated carboxyl groups there were on CNFs, the more negative charge it carried, which was conducive to the adsorption of strongly charged MB. Hg(II) elimination by the pure carboxylated CNFs film rose from about 5 % at pH 4 to 54 % at pH 11 in an aqueous solution with a starting Hg(II) concentration of 50 g/L [155]. The surface charge of CNFs became increasingly negative as solution pH increased, and the zeta potential declined from −6.6 1.1 mV at pH 4 to −17.6 0.6 mV at pH 11.

Nano-cellulose-based adsorbents and adsorbates can be incorporated using coordination bonds for the formation of complexes. Complexation involved the use of cation to combine with anionic molecules with pair of free electrons also known as ligands [156]. In the case of central atom association with two or more ligands atom, the formed complex ring structure is known as chelate. Deprotonated carboxyl groups involved for the formation of complex between the cationic dye and metal ions. The FT-IR spectra revealed that CNCs carboxyl groups form complex with metals ions, and Cd (II) or Pb (II) get the combination with carboxyl groups with forming bidentate chelating structure [157]. For NC porous membranes synthesis from CNC electro spun fibres and polyacrylamide, when the amide groups were partly transform into carboxylates using hydrolysis process, the derived anion polyacrylamide gels adsorb cationic dyes including MB [158].

Metal ions can also form complexes with thiol groups and other S-ligands retained by the adsorbent. The chromate adsorption capability of the thiol-modified CNF film was 2- to 3-fold that of the original CNF film [159]. This is due to the creation of a Cr (VI)-thiolate complexion. The chelation of thiols and amino groups to mercury ions was used to achieve Hg(II) adsorption on L-cysteine-functionalized cellulose NFs [160]. Metal ion-S group complexation occurs between metals and S-ligand-linked CNFs [161]. Because $SC(NH_2)_2$ exhibited a diffuse electron cloud, S ligands bonded well with Pb (II) and Cd (II) ions.

Metal cations or cationic dyes replace the cations in the ligands and form complexes via the ion exchange process of adsorption [162]. Furthermore, anionic dyes can be employed as ligands to substitute anions in the adsorbent [163]. Ion exchange occurs largely in carboxyl and hydroxyl groups. The cationic Co(II) adsorption process by the poly (itaconic acid/methacrylic acid)-grafted-nanocellulose/nano-bentonite composite comprised ion exchange followed by complexation [164]. The equilibrium pH was lower than the starting pH in the adsorption equilibrium investigation, indicating that a cation exchange route occurred during the Co (II) process of adsorption. The infrared spectra of Co(II)-adsorbent revealed a peak at 940 cm^{-1}, confirming the production of Co(II)-O. Metal ion M (II) might react with surface hydroxyl groups via a Si-O-M-O-Si bridge in the reaction with 3-aminopropyl-triethoxysilane, and M(II) could also react with an amine group and exchange with a neighbouring hydroxyl group [165].

The π-π interaction is a non-covalent contact that takes place predominantly between aromatic rings. The π-π interactions developed between polydopamine(PDA) and the aromatic ring of MO dye particles in the PDA-CNF aerogels [166]. The process of adsorption for the magnetic nano-cellulose-based polymeric ILs included π–π interactions between bulk structures on the imidazolium ring and CR dye molecules [163]. The π-π stack interactions formed within the aromatic rings of the dye and the imidazolium residues in the imidazolium-grafted CNCs [167].

5.1.2. Kinetic study

Mass transfer, Diffusion control and chemical reaction are some of the mechanisms used to control the adsorption process, and these processes are useful for developing kinetic models [168]. When determining the ideal conditions to run a batch operation at full scale, dye adsorption kinetics are critical [168–170]. The adsorption kinetic study of shows how the rate of solute uptake influences the time of residency of the adsorbate at the solution interface. When the adsorption process is developed and computed based on the kinetic studies, this rate becomes significant [171]. Sorption energy is critical for determining the best working conditions for sorbent-sorbate interaction and is a crucial factor in mapping the sorption process. As a result, pseudo 1st and 2nd order kinetics models, along with intra-particle models, are explored to estimate the sorbent efficiency and to study the regulating constituents of the sorption. AR-42 dye removal on CMC/O-bent composite performed with pseudo- 2nd order kinetics [172]. Based on predicted and actual data, the kinetic analysis of organophilic composite montmorillonite/CA to eradicate Eosin Y followed the pseudo-2nd order vs. the pseudo-1st order [173]. Additionally, the pseudo-2nd order kinetic model well fitted the CR dye elimination significantly [174] .

Also, Mohammed et al. [175] studied the sorption kinetics of MB dye using beads of composite CNC-alginate hydrogel using intraparticle diffusion, pseudo-1st and 2nd - order models. The pseudo-2nd order kinetics and intraparticle diffusion model best characterized adsorption kinetics and mechanism. The R^2 (regression coefficients) values for pseudo-1st order kinetics were lower than those for pseudo- 2nd order kinetics. The pseudo-2nd order kinetics fitted model perfectly (R^2,0.99). Similarly, Kausar et al. [176] studied the sorption kinetic data for dye

Drimarine Yellow HF-3GL onto the composite cellulose and clay were studied using a pseudo 2nd order kinetic model. Liu et al. [177] studies the sorption kinetics studies for MB and acid blue 93 dyes from binary and single systems using adsorbent prepare from cellulose using pseudo 2nd - order. The R^2 values for MB and AB-93 dyes in the pseudo-2nd order kinetics model were 0.9980, which was higher to R^2 values of pseudo-1st order model.

5.1.3. Thermodynamics study

Temperature is an important aspect in the color adsorption process. Wastes from industries are emitted at different temperatures, which must be researched in order to comprehend the adsorption characteristics of adsorbates. It is beneficial to analyze the adsorption process thermodynamically in order to build effective adsorbents [171]. Temperature and adsorption properties can be utilized to predict distinct thermodynamic parameters including ΔH°, ΔS°, and ΔG° [178]. The provided data describe the exothermic and endothermic characteristics of dye adsorption onto cellulose-based adsorbents using thermodynamic analysis. Endothermic processes occur when the adsorption rate improved with increasing temperatures. It happens because when temperature rises, the mobility of dye molecules increases, making more availability of adsorptions active sites. Similarly, decline in adsorption rate with elevation of temperatures resulted to develop the exothermic process. The explanation for this drop in adsorption is a decrease in attraction forces between the adsorbent's active sites and the dye species [179].

Thermodynamic properties provide information on energy changes that occur throughout the adsorption process. At various temperatures, the values of ΔH° and ΔG° were positive and negative, representing that adsorption occurred spontaneously as an endothermic process. Positive ΔS° values indicate a high affinity between adsorbate and adsorbent, indicating a higher degree of unpredictability at the interface of adsorbent-solution [180].

Zhou et al. [181] studies over eradication of anionic dyes using CA/organo-montmorillonite (OMMT) composite. The results suggested that the process with spontaneous and endothermic because the standard enthalpy change following sorption of Acid Scarlet G with CA/OMMT 60 % giving energy value of 24.8 kJ/mol. Negative ΔG° values for Congo red adsorption onto Na-rich montmorillonite at different temperatures show spontaneous sorption behaviour. Endothermic sorption was revealed with positive ΔH° values. A positive ΔS° value represented higher chance of unpredictability at the solution-solid interface [174].

The negative ΔG° value was obtained at various temperatures using binary and single sorption methods on the dyes [crystal violet (CV) and methyl blue (MB)] using composites of cellulose/calcium alginate, represented the MB and CV adsorption as the spontaneous process, and the ΔH° value were negative for both dye and represented exothermic nature of reaction [180] . Similarly, Mohammed et al. [182] performed experiment with removing anionic dye using composites of CNC-alginate hydrogel beads. By increasing the temperature from 25 to 55 °C, dye removal was lowered from 77 to 69 %. Negative ΔG° values show the sorption process's spontaneity. In the case of temperature elevation, ΔG° rose as well, demonstrating that adsorption decreased with temperature. Negative ΔH° values indicate that the adsorption process was exothermic. Thermodynamic investigations reveal that the sorption of dyes onto cellulose-based adsorbents can be exothermic or endothermic.

5.2. Cellulose-based membranes

The following techniques are typically used to process nano-cellulose membranes: (I) functionalized nano-cellulose impregnating electro-spun mats [183]; (II) vacuum filtration and coating [184]; and (III) direct deposition of solution [185]. After being modified, nano-cellulose is employed to support membrane structure or as an active adsorption substance. By modifying the composition of the support layer of sludge micro-fibrils/CNFs and in situ carboxyl functionalization of the CNC thin functional layer, [185] produced membrane-based nano-cellulose with improved water permeability, mechanical stability, and enhanced adsorption capacity of metal ions. A schematic illustration of the processing of support layers and membranes is shown in Fig. 2. To create sulfhydryl-functionalized nano-fiber composite membranes, cysteine was grafted onto oxidized CNFs embedded in electro spun polyacrylonitrile nano-fibrous scaffolds. These membranes are employed as a high-flux microfiltration filter (1000 L/m^2h/psi) [159].

5.3. Cellulose-based aerogels

Aerogels are derived from materials such as organic polymers and inorganic particles, and because polymer-based aerogels are often physically flexible, they can maintain their integrity after adsorption [186]. Utilizing sustainable polymers instead of petroleum-derived ones with a large carbon footprint is current preparation strategies for aerogel production [187]. The most prevalent natural polymer on earth is cellulose, which makes it an appealing material for making bio-aerogels [11,188]. With its higher aspect ratio, sizable surface area, and plentiful hydroxyl groups, CNF has drawn increased interest in the creation of cellulose aerogel [189]. Additionally, aerogels derived from cellulose have recently been identified as efficient adsorbents for the removal of heavy metal ions, such as Cu(II), Pb(II)and Cr(VI), among others [190]. However, because pristine CNF lacks the sites of adsorption for Cr(VI), it makes sense to create an amine-functionalized cellulose aerogel to enhance that material's capacity to bind Cr(VI). The durability of CNF and the strong affinity between Cr (VI) and the amine group are also advantages of this tactic.

The cellulose-based aerogel adsorbent was effectively made employing an innovative crosslinking technique for removing the static and dynamic dye, and transesterification process were followed for cellulose acetoacetate and -cyclodextrin acetoacetate, subsequently cross linked with the polymer chain of polyethyleneimine resulted to form dynamic enamine bonds and freezing drying was performed to three-dimensional structural network [191]. At 25 °C, the highest adsorption rate for methyl orange (MO) was 1013.11 mg/g.

6. Cellulose-based materials for removing pollutants from wastewater

6.1. Removing heavy metals, dye, and other pollutants

Due to heavy metal ions' non-degradability, carcinogenicity, and high toxicity, heavy metal ion contamination of water has also grown to be a severe issue in recent years [192,193]. Another unpleasant form of pollution that comes from various industrial sectors, including the cosmetics, textiles, paint, plastics, and paper industries, is pollution caused by dyes [194]. By the end of 2010, >700,000 tons of dyes had been manufactured, and there are currently about 100,000 commercial dyes known to exist [4]. Sewage treatment poses a significant environmental and economic challenge today. As a result of its practicality and effectiveness, adsorption is regarded as a universal method for scavenging heavy metal ions [195]. The process following Cr(VI) adsorption, reduction, and sequestration is recommended. Aerogel has distinct benefits in terms of its high surface area and faster separation approach when compared to many other types of adsorbents, which is promising for the removal of water contaminants [186]. The Cr(VI) is available in anionic forms ($HCrO^{4-}$ and $Cr_2O_7^{2-}$) at pH >2.0, therefore, the design of aerogels with positive charged groups is an appropriate approach to Cr (VI) adsorption [196]. Recent studies have shown that amine groups have the capacity for the adsorption and reduction of Cr(VI) while maintaining acidic conditions [197], For the effective removal of Cr(VI), it is therefore highly desirable to produce amine-functionalized aerogels. There are various possibilities for the effective treatment of different contaminants among the standard methods used for pollution

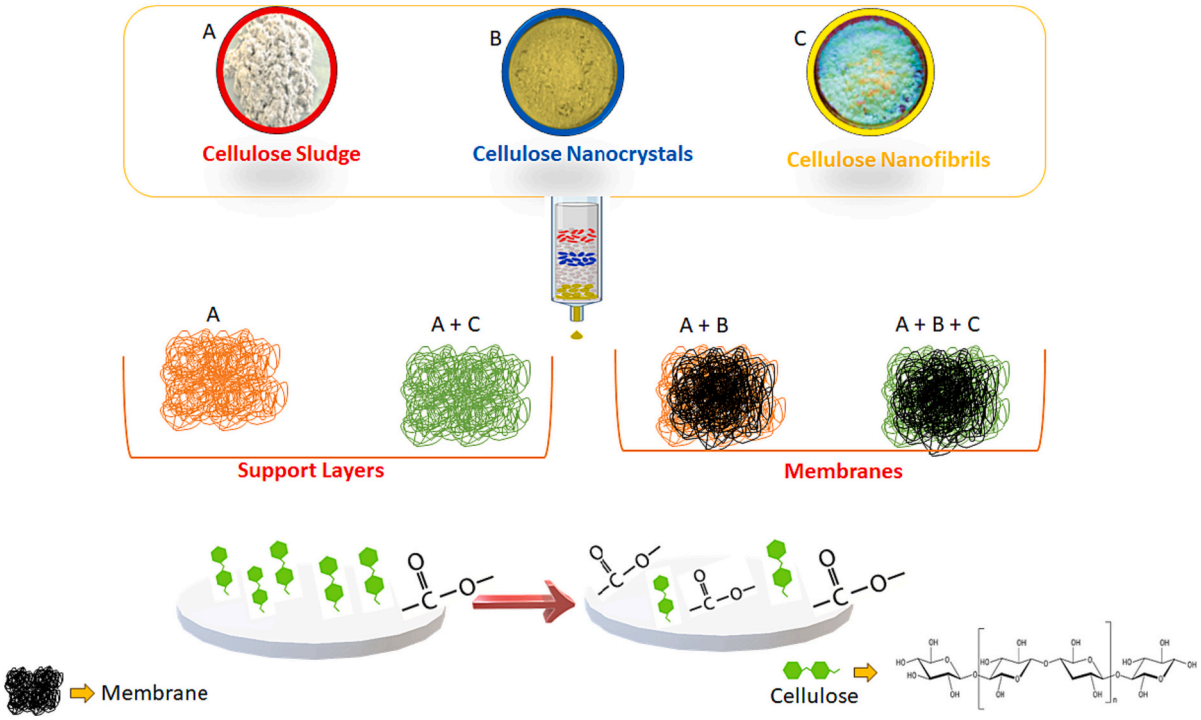

Fig. 2. Processing system for support layers and membranes.

control. Due to its simplicity, high efficiency, and straightforward and ideal performance, adsorption technology has been extensively applied in dye treatment. Utilizing solid-liquid two-phase separation, the biomass adsorption method uses the chemical makeup and structure of biomass materials to absorb chemical contaminants present in water. Hydrogen bonds, Van der Waals forces, hydrophobic interaction, dipole induction, polar and spatial interactions, dipole and other physical phenomena are among the principal physical forces regulating the adsorption of cellulose-based adsorbents in addition to chemisorption's [198]. The presence of cellulose hydroxyl groups on the surface makes it easy to modify, and it's long, thin, and many threads are useful for creating mesh structures that can later become porous. Biomass materials with natural porosity have been extensively researched to create structures for the absorption of oil droplets from water [199]. Additionally, Jiang et al., [200] used the cellulose-based adsorbent for removing Congo red.

The Taguchi robust design employed optimize the elements determining the efficacy of heavy metal eradication, namely ion concentration, the pH-value, contact time, and adsorbent dosage were the parameters for the study. The batch experiment for absorption was performed using an orthogonal array (OA) [201]. According to contour plots and verification tests, the optimum conditions for Co (II) and Cs (I) adsorption was pH (5–6), concentration (1–50 mg/L), dosages (3–4 g/L), contact time (60–100 min), where the % of eradication achieved was 74 and 88 % for Co (II) and Cs (I), respectively, under mention optimum conditions.

The N-doped cellulose-based hydrothermal carbon (N-CHC) contains a large number of O and N groups that are favourable for Cr (VI) reduction and adsorption. Intermittent adsorption studies revealed that N-CHC adsorption performance for Cr (VI) was 151.05 mg/g at pH 2, showing outstanding adsorption performance [202]. According to kinetic and thermodynamic assessments, Cr (VI) adsorption on N-CHC was governed by a monolayer uniform adsorption mechanism, with following spontaneous endothermic process and interaction were dominated by chemical nature and least by diffusion phenomena. The N-CHC was selective and toward Cr (VI) was 82.62 % when compared with others ions including Pb^{2+}, Mn^{7+}, Cd^{2+}, Cl^{-}, and SO_4^{2-}. Furthermore, across seven adsorption-desorption cycles, N-CHC displayed remarkable reuse performance; the Cr (VI) eradication rate of N-CHC at the concentration of 5–20 mg/L in wastewater (>99.87 %), demonstrating N-CHC's potential for large-scale applications.

Adsorption is a process that increases entropy and is endothermic, according to thermodynamic characteristics. The chemosorption of colors on biomass adsorbents removes organic contaminants from the aqueous environment. The electrostatic interaction was involved between Congo red and adsorbents during the process of adsorption. It has been reported that biological sorbents made from sugarcane are utilized to eliminate pollutants. These have a variety of functional groups, including -COOH,-SH $-OCH_3$-OH, $-NH_2$, and $-CONH_2$ which aid in chelating, complexing, coordinating, and hydrogen bonding to draw and binds the contaminant ions at the site of adsorption [203].It has also been observed that the adsorbent made from biomass materials may remove color from sewage [204]. The dye types, the aqueous environment in which the dye is situated, and the adsorbent functionalization are the key variables influencing the dye adsorption by biomass [205]. As a result, the modified biomass material's high affinity for the dye can greatly increase its adsorption capacity (Table 2A).

Experiments were carried out in different solutions of ionic strength &pH to look at the interaction of MO dye with the MF-CNCs surface [215]. These studies are crucial to clarify the adsorbent's effectiveness in waste streams that comprise different chemical species. Fig. 3A and B illustrates use of MF-CNCs to remove MO, and respective MF-CNCs zeta potential at various pH. By examining the pattern in relation to zeta potential (Fig. 3B), it is possible to explain the trend in on the decline of dye removal percentage with the elevation of pH (Fig. 3A). Between pH 2 and 9, the MF-CNC's zeta potential was positive (>+30 mV), however, it drastically dropped to 9.67 mV at pH 11. Other researchers have discovered that there were higher positive charges at lower pH [216,217] which are connected to the protonation of the secondary and primary amines on the surface of MF-CNC. As a result, these functional groups' deprotonation at higher pH produced an increasing amount of surface charge with negative groups [216,217], and the trend of dye removal percentage fell with elevation of pH. The fact that the presence of charged sulphonate groups with negative ions in the MO indicates

Table 2A
Different biomass materials involved in dye adsorption.

Method	Pollutants	Sorbent	Effects of separation (mg/g)	References
Coagulation precipitation	Congo red	Cellulose	66.09	[206]
Activation	Methylene blue	Lignin/chitosan *co*-polymer	36.25	[207]
Chemical modification	Methylene blue	Bamboo	606	[208]
Carbonized	Methylene blue	Grapes	417	[209]
Boil	Methylene blue	Potato leaf and stalk	52.6 and 41.6	[210]
Chemical crosslinking	Methylene blue	Cellulose/clay hydrogels	98	[211]
Amino functionalization	Acid red	cellulose	555.6	[212]
Surface quaternized	Congo red	Cellulose	498	[213]
Citric acid modification	Methylene blue	Wheat straw	396.9	[214]

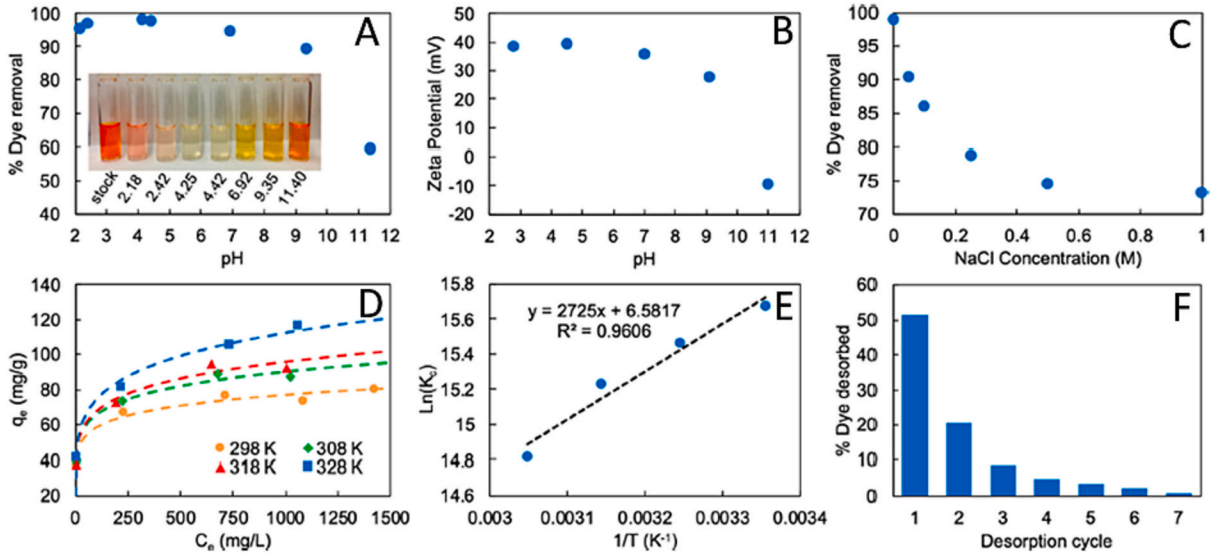

Fig. 3. Effect of methyl orange (MO) solution pH, ionic strength, temperature, and acid addition on MO dye removal. (A) solution pH on MO dye removal, (B) effect of solution pH on zeta potential of MF–CNC, (C) effect of solution ionic strength on MO dye removal, (D) effect of temperature on MO dye removal, (E) van't Hoff plot of MO adsorption temperature, and (F) 1 M HCl to desorb MO from MF–CNC with % dye desorbed corresponding to percentage of initially adsorbed dye desorbed in that stage. In panel A, insert images illustrates the stock solution and equilibrium samples at each pH. MF–CNC, melamine formaldehyde-functionalized cellulose nanocrystals. Panels (A–F) are reproduced with permission (copyright © 2020 American Chemical Society, Washington, United States) from Grishkewich et al. [215].

that electrostatic interactions are very important for the adsorption of MF-CNC. This theory is supported by decreasing the dye loss percentage at elevated pH with the absence of negatively charged ions on the MF-CNC surface. The investigation for ionic strength of the solutions on removing the dye is required to further support the adsorption theory-based one-lectrostatic. Fig. 3C uses various ionic strength solutions using NaCl concentrations and strength for scavenging the dye. Long-range electrostatic interactions were involved between adsorbent and adsorbate molecules after the addition of NaCl to the MO solution. When the concentration of NaCl was increased from 0 to 1 M, the percentage of dye removal fell from 99 to 73 %, indicating that electrostatic interaction facilitates the adsorption of MF-CNC on MO. Contrarily, with the elevation in NaCl concentration from 0 to 1 M, the adsorption by CNC alginate beads for methylene blue decreased from 75 to 5 %. This implies that factors other than electrostatic interaction affect the MO adsorption on MF-CNC. Therefore, this method is suited for water treatment because of the ease and low cost of production for its used in removing the impurities. Fig. 3D depicts the relationship between temperature and the adsorption isotherm for temperatures between 25 and 55 °C, demonstrating that higher temperatures encourage adsorption. The resultant van't Hoff plot is shown in Fig. 3E.

The substantial negative ΔG° (Gibbs free energy) values, which ranged from 38.9 to 40.4 kJ/mol, supported the conclusion that adsorption is more favourable at elevated temperatures with greater negative ΔG° values. Additionally, the exothermic nature of the adsorption process was corroborated by the negative value for ΔH° (enthalpy) that was retrieved usingthe van't Hoff plot. The fact that the entropy increased shows that, despite the MO losing its freedom after attaching to the adsorbent's surface, the MF-CNC adsorbent and solvent underwent changes that led to a net gain in entropy [218]. The amount of ΔH° may indicate the physisorption adsorption process(8–65 kJ/mol H°) or chemisorption (84–420 kJ/mol H°) [219]. The size of ΔH° discovered during this analysis provided more evidence that the adsorption is physisorption. The sign and magnitude of ΔH° indicated the physisorption, which is an exothermic process, and the process can be anticipated as endothermic adsorption with the rise of the adsorption process with temperature [220]. Higher temperatures may also help the adsorption capacity rise since MO is more mobile at higher temperatures [221]. Fig. 3F displays the outcomes following the application of 1 M HCl eluent to desorb MO from MF-CNCs in a series of cycles. 25 % of the MO adsorbed followed the desorption process from the MF-CNC after the initial round. The MO was adsorbed initially, and 92 % of the adsorbed were desorbed, proving that the MF-CNC could be regenerated and used for additional adsorption operations.

Cell-EDTA and Cell-CM, which were employed as adsorbents for heavy metal ions were developed by extracting cellulose fiber from the leaves of pineapple and added ethylenediaminetetraacetic acid (EDTA) and carboxymethyl (CM) groups, respectively (Fig. 4). The wastewater used to examine adsorption efficiency was either a solution of Pb^{2+} or Cd^{2+}. Cellulose fiber from pineapple leaves was separated and subjected

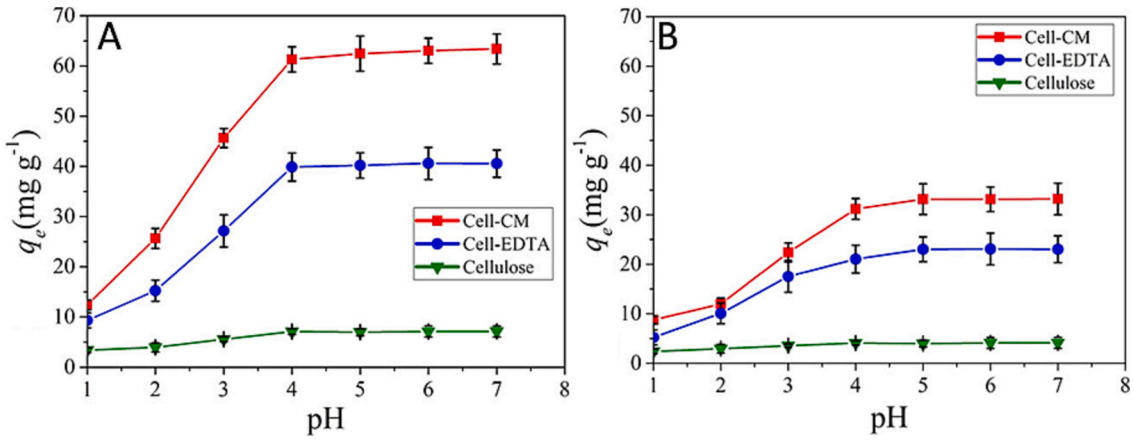

Fig. 4. Adsorption efficiencies (q_e) of cellulose and modified cellulose for (A) Pb^{2+} and (B) Cd^{2+} at pH 1–7. Cell-CM, cell treated with carboxymethyl; Cell-EDTA, cell treated with ethylenediaminetetraacetic acid. Panels (A and B) are reproduced from Daochalermwong et al. [222] and is an open access article (copyright © 2020 American Chemical Society, Washington, United States) distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license.

to treatments with EDTA and CM groups, respectively, to create Cell-EDTA and Cell-CM, which were involved in the adsorption of heavy metal ions. Water contained solution of the lead ion Pb^{2+} or Cd^{2+} to test the effectiveness of adsorption. According to Daochalermwong et al. [222] the materials were further described using FT-IR measurement following Pb^{2+} or Cd^{2+} adsorption. The spectra were evaluated against those discovered before adsorption. As the extracted cellulose's has exceptionally low metal ion adsorption, for which all of the bands in the samples for the extracted cellulose were surprisingly similar to those prior to adsorption. It was evident that the bands showing the O=C−O representation of the EDTA group (1588 cm^{-1}) and the band showing the C═O stretching of the carboxyl group (1727 cm^{-1}) almost vanished for Cell-EDTA and Cell-CM, suggesting that the EDTA or CM group was involved in the coordination [223]. The normal observational range for Pb—O and Cd-O's distinctive absorption bands is 700–400 cm^{-1} [224]. However, they were underlying with the adsorbents' absorption bands, making it challenging to distinguish them. Similarly, Daochalermwong et al. [222] investigated the impact of the metal ion solutions' pH on the modified celluloses' adsorption effectiveness, and a comparison with the situation of the extracted cellulose. The pH range used for the study ranged from 1 to 7. It is evident that the pH range between 5 and 7 corresponded to the maximum efficiencies of adsorption from extracted cellulose, Cell-EDTA, and Cell-CM. In more detail, Cell-EDTA had maximum adsorption efficiencies of around 40 mg/g(Pb^{2+}) and 33 mg/g (Cd^{2+}), whereas Cell-CM had maximum adsorption efficiencies of about 63 mg/g (Pb^{2+}) and 23 mg/g (Cd^{2+}). The maximal adsorption efficiencies of the extracted cellulose, at around 7 mg/g(Pb^{2+}) and 4 mg/g (Cd^{2+}), were much lower than those of Cell-EDTA and Cell-CM. Because the quantity of protons in the solution changed for pH values between 1 and 3, the adsorption efficiencies of all three samples dropped with falling pH values. The metal ions had to contend with protonation of the carboxyl and carboxylate groups as the quantity of protons grew (by lowering the pH) and thus raised the positive surface charge of the adsorbent [225]. In further studies, a pH of 6 was recommended since, at higher pH levels, changing pH had no impact on efficiency. It should be noted that the precipitation of the metals' hydroxide forms precluded the measurement of adsorption with metal ion solutions above pH 7.

6.2. Cellulose-based membranes

Through electrospinning and curing, Ertas et al. [226] developed nano-fibrous membranes made of a CA/polybenzoxazine composite. An ideal membrane material for water filtration is polybenzoxazine, a thermoset resin with a phenolic group having different desirable characteristics, including nearly curing resulting in zero volumetric change, zero by-products, curing done in the absence of catalysts, reduced water absorption, retaining a higher glass transition temperature, high char yield, and better thermal and mechanical characteristics. Citric acid was utilized as a second cross-linking agent in order to effectively solve the solubility issue. The membrane generated from nanofibrous was able to maintain its fibrous morphology and integrity even after dipping overnight in the dichloromethane/methane mixture of solvent, in which electro-spinning was carried out, because of this cross-linking feature. The electrospun CA/polybenzoxazine composite nano-fibrous membrane was characterized, and it was shown to be a very sustainable membrane for the filtration of water and the treatment of sewage. By using the phase-inversion method to construct the chitosan/CA composite, Ghee et al. were able to create the nano-filtration composite membrane [43]. Their efforts produced a membrane that was extremely porous, had channel-like features, and had a spongy layer on top. The composite membrane had exceptional mechanical stability thanks to the substrate membrane's 15 wt% CA content, which also enabled the largest water flux. This composite membrane's retention, water flux, hydrophobicity, regeneration effectiveness, and antifouling features were all enhanced by the addition of chitosan.

When used as a reinforcement material, nano-diamond nanoparticles (ND-NP) can give the surface of CA good thermal and mechanical qualities, better hydrophilicity, and a very high specific surface area [227]. By inserting the unprocessed and thermally functionalized ND, ND-COOH, into CA, the effect of NPs on the functionality, morphology, hydrophilicity, and fouling behaviour of CA membranes in water treatment was examined. The CA/ND-COOH (0.5 wt%) membrane had the best abrasion resistance, pure water flux, hydrophilicity, and mechanical qualities, according to the final analysis. Despite all of ND's benefits, the occurrence of carbon impurities and the development of small aggregates may cause poor dispersibility and ineffectiveness of the polymer matrix with interfacial interactions. The CA-NC membrane demonstrated strong hydrophilicity, porosity, and high anti-bio-fouling capabilities when it was combined with amino (NH_2)-functionalized as well as polyethylene glycol (PEG)-grafted NDs [228]. Silver was added to CA in two different forms, PVP-coated silver nanoparticles (Ag-NPs) and silver ion exchanged zeolite (Ag^+Z), to create a flat-sheet nano-filtration membrane with bactericide characteristics [229]. A composite nano-filtration membrane with improved hydrophilic properties and a higher removal coefficient for sulphate salts (Na_2SO_4, $MgSO_4$) than for chloride salts (NaCl, $MgCl_2$) was produced as a result of this research. In addition, the CA/Ag^+Z membrane's hydraulic permeability was 56.3 % higher than it was for the CA silver-free membrane. A core/shell-structured CA/polyimide(PI) electro-spun fibrous membrane can be created using the electro-spinning technique, and it is then altered by

fluorinated benzoxazine (F-PB) in the presence of silicon nanoparticles (S-NPs) [230].The resulting nano-fibrous membrane has the surface roughness of the CA shell and the mechanical properties of the PI fiber core. Additionally, F-PB/SNP surface alterations gave the membrane superhydrophilicity and super leophilicity. With consistent ultrafiltration uses, CA membranes enhanced with ZnO have shown improved hydrophilicity and permeability [231]. The phase-inversion technique was used to create a CA/hydroxyapatite (HA) composite for water filtration. Hazardous chemicals like Cr(VI), Ni^{2+}, and Cd^{2+} were removed from aqueous solutions using hydroxyapatite [232]. Limitations like low production yield and a slow rate of hydroxyapatite nanoparticle degradation are overcome by the inclusion of hydroxyapatite nanoparticles into polymers, which also increases their dispersion on the surface of the polymer substrate. By using electro-spinning, Hamad et al., [233] created a hybrid nano-fiber composite CA/HA with ultrafine, smooth, homogenous, and bead-free fibres. The carboxylate groups, as negatively charged groups in CA, are connected to the positively charged calcium ions. Intermolecular and intramolecular interactions can also result in a composite membrane that is HA-rich. These qualities boosted production and reduced HA's rate of degradation. Using BC as separation membranes in a variety of applications, Alves et al. [35] looked into their application in the separation of PEG, and Wanichapichart et al. [234] effectively filtered bovine serum albumin and *Chlorella* sp. using BC. It has been demonstrated that BC treatment with AA is effective at removing metallic ions, including heavy metals [235].For the elimination of Cr(VI), Taha et al. [236] developed CA/silica composites that have been NH_2-functionalized. Trimethylchlorosilane was used by Sai et al. [237] to create aerogels of modified BCs that could absorb up to 185 times their own weight in oils and organic solvents from the environment. In their study, El-Wakil et al. [238] investigated the use of BC in removing oil from emulsion of oil-in-water. A filter made of BC get modification after adding isolated soy protein to remove airborne particles [239]. This research generates neoteric upliftment and the approaching relevance of graphene oxide–CNC, nano-filter composite membrane (NFCM) for eradication of Cr^{3+}, Ni^{2+}, Cd^{2+}, Pb^{2+}, Co^{2+} and MB dye from wastewater derived from industry [169,240]. The produced NFCM were extremely crystalline, thermally stable, had good surface activity, and demonstrated exceptional eradication effectiveness against hazardous dye and heavy metals. The research was carried out to describe a simple yet environmentally acceptable method for producing a superhydrophobic, oil/water separation, anti-bio-adhesion, and photocatalytic Pulp/CNFs membrane for all purpose treatment of wastewater [188,241,242]. The micro/nano-structured CeO_2 nanoparticles and stearic acid (STA)-coated Pulp/CNF (Pulp/CNF-CeO2-STA) membrane was developed using a simple and easy-to-use coating method, the developed membrane performed with super wettability, enhanced separation capacity of oil/water, acceptable capacity for photocatalytic degradation with functioning anti-bio-adhesive properties. The constructed membrane had superior super-hydrophobicity (water contact angle: 166 2°), greater separation efficiency (88 %) [241]. The photocatalytic breakdown of organic dye pollutants in water by the membrane was similarly significant (>94 %).

6.3. Cellulose-based flocculants

The removal of tiny suspended solid substances, metals, colors, and other organic substances from wastewater utilized in the municipal and industrial sectors is commonly accomplished through flocculation. Flocculants are added to the solution to encourage the collision of colloidal particles, resulting in the formation of bigger, unstable particles known as flocs that eventually precipitate out of the mixture. These flocculants can occasionally lead to the creation of larger flocks by bridging and electrostatically interacting with colloidal particles [243]. Because of its many characteristics, CNFs are good options to employ as flocculants [244]. As a result, recent studies using CNFs as flocculants have produced some fascinating findings, some of which are discussed here. A few CNs-based flocculants employed for flocculation of water pollutants is shown in Table 2B. All of these studies have demonstrated the benefits of employing cellulose-based nano-cellulose as flocculent, providing safe, environmentally friendly substitutes for polymers generated from petroleum. These CNCs' ability to flocculate made them an efficient flocculent for water treatment, lowering the turbidity of wastewater. Nevertheless, a lot of these discoveries are applied in lab settings; therefore, more research is necessary to expand these discoveries to a commercial scale. Fig. 5 shows the nine Scopus and JCR-indexed journals with the most publications in this field. Carbohydrate Polymers, Journal of Applied Polymer Science, and Cellulose have >15 articles apiece, and are closely tracked by the Journal of Membrane Science, which has >10 publications. Except for Journal of Applied Polymer Science, which belongs to the second quartile despite maintaining a high h index of over 150 at the end of 2020 (SJR), the aforementioned journals are part of the first quartile in the area of research that covers the publications considered in 2019, except for Journal of Applied Polymer Science, which is in the second quartile despite maintaining a high h index of >150 at the end of 2020 (SJR). In general, the effects of factors are unrelated to the number of publications. In any instance, the total number of articles in the same range of impact factors is higher for the journal whose scope handles the issue more specifically. Microwave-assisted copolymerization was used to create terpolymer with an anionic groups using carboxymethyl cellulose-sodium alginate -itaconic acid [245]. The flocculation properties of crystal violet (CV) dye were investigated. With a terpolymer content of 30 mg/L, the maximum eradication rate of 100 mg/L (CV) for wastewater was 92.20 %. Similarly, hydrothermal copolymerization was used in another investigation to create a ternary anionic flocculant composed of xanthan gum, AM, and carboxymethyl cellulose [246]. For the 100 mg/L CV dissolving solution, a decolorization ratio of 82.9 % was achieved with a composite dosage of 35 mg/L. The as-prepared flocculants demonstrated excellent decolorization and rapid flocculation kinetics. The cationic cellulose (CC) sample was examined in three environmental applications as a flocculant or sorbent: algal harvesting, removing solids for dairy WW, and captured MO dye in wastewater [247]. As measured by absorbance at 463 nm, approximately 64.2 % of the MO was sorbed from WW got eradicated by CC.

6.4. Cellulose-based on water filtration

A membrane for water filtration is used to remove impurities from water by excluding particles with charge- mediated adsorption phenomena. Cellulose is used in some water-filtering membranes due to their larger surface area, better mechanical strength, and nanoscale size. Materials based on nano-cellulose can function as filter membranes, or adsorbents, depending on the pore shape and mode of action. The efficiency of membranes based on nano-cellulose is determined by the ability of high-surface-area nano-cellulose fibres to selectively absorb

Table 2B
Cellulose-based flocculants used for the flocculation of water contaminants[a].

Contaminants[a]	Cellulose based flocculants	References
Dyeing wastewater	CMC-g-PAM graft co-polymers	[248]
Silica nanoparticles	Cationic cellulose-based polymers derived from Eucalyptus bleached fiber ($CDAC_f$)	[249]
Turbidity and ink	NC combined with a cationic PAM	[250]
Turbidity and SiO_2	Cationized CNC with EPTMAC	[251]
Kaolin clay suspension, dyes, and heavy metals	CNFs	[252]
Anionic dye	CMC-g-PDMC graft co-polymers	[253]

[a] EPTMAC, Epoxy-propyltrimethylammonium chloride; NC, Nanocellulose; CNFs, Cellulose nanofibers; SiO_2, Silicon dioxide; CMC-g-PAM, carboxymethyl chitosan-*graft*-polyacrylamide; CMC-g-PDMC, carboxymethyl cellulose-*graft*-poly[(2-methacryloyloxyethyl) trimethyl ammonium chloride].

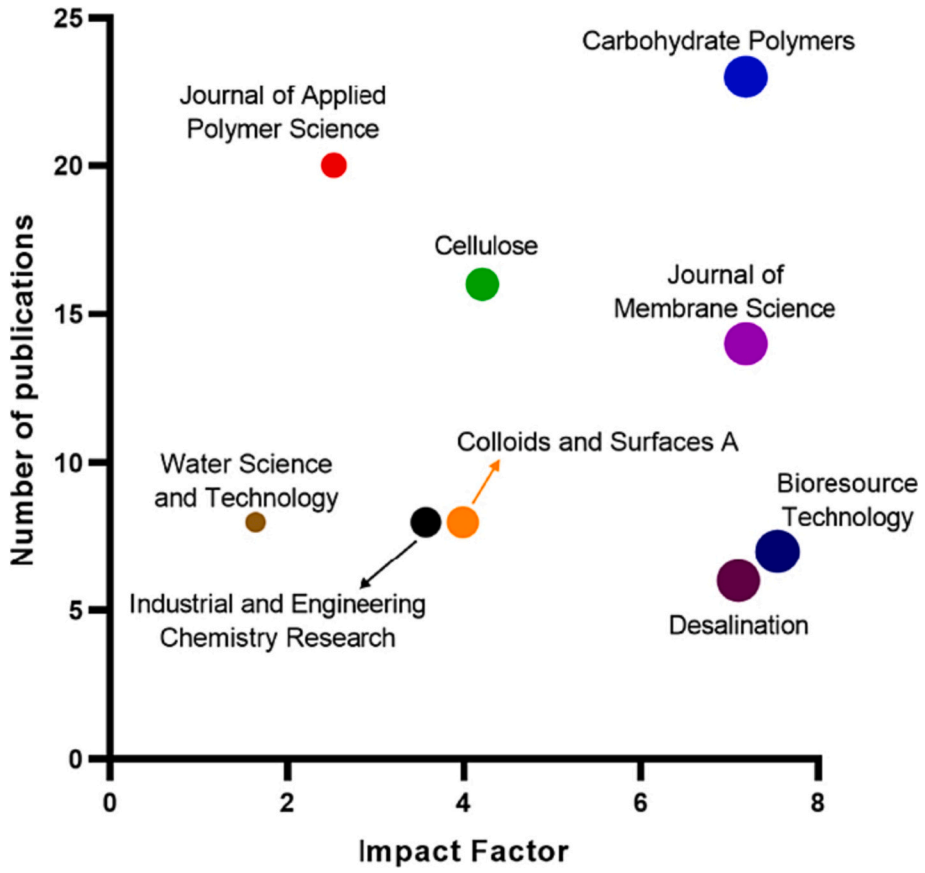

Fig. 5. Publications on the application of cellulose as flocculants and coagulants as of 2020. This figure is reproduced from Barrero-Fernández et al. [254] and is an open access article (copyright © 2021 by authors) distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license.

pollutants from WW. Identical adsorption of contaminants is facilitated by the presence of functional groups on the nano-cellulose surface, including amidation, sulfonation, etherification, carboxylation, esterification, phosphorylation, silyation, and TEMPO -mediated oxidation. Because of their natural hydrophilicity and controlled surface chemistry, nanomaterials can reduce organic and bio-fouling, two problems seen in membrane technology. Polymer composites and pure CN mats are used in the production of CNF-based membranes. Membrane distillation, nano-filtration, ultra-filtration, micro-filtration and other similar membrane separation techniques have all made use of CNF-based membranes. Nanocellulose was used in the fabrication of different filtration membranes, including reverse membranes and microfiltration membranes [255]. For example, [256], employed CNF in the filtration procedure to construct a membrane. They created ultra-filtration membranes by using CNCs on both sides of the membranes to eradicate metal ions including Fe^{2+}, Fe^{3+}, Ag^{+}, and Cu^{2+}. The membranes performed with remarkable ability to remove ions from industrial WW (100 %). The features of the membrane, including its porosity, pore size, tensile strength, permeability, selectivity, surface hydrophilicity and resistance to bio-fouling, are considerably altered by the presence of CNFs in the internal regions of the polymer matrix [63]. Hanif et al. [257] used the TA-mediated silver salt layer-by-layer (LbL) in-situ reduction approach to create a non-toxic and environmentally friendly process. These hybrid membranes with Ag-NPs deposited in LbL demonstrated exceptional antibacterial activity and successfully filtered the *E. coli* germs.

6.5. pH responsive cellulose composites

During oil-water separation, pH-responsive cellulose composites can be employed. For instance, by grafting AA and AM, respectively, onto eucalyptus pulp cellulose, two pH-responsive reversible-wettability biomass cellulose-based materials, cellulose-g-**PAA** and cellulose-g-**PAM**, were created [258]. The membranes were made pH-responsive by the AA and AM functional moieties. These moieties also gave the membranes a hydrophilicity that was pH-responsive. The membranes' hydrophilic nature gave them anti-fouling qualities, which significantly improved how well they performed. These pH-responsive composites were employed to separate the oil from the water. These cellulose-based composites' hydrophilicity and oleophobicity were pH-dependent. At pH 1, the amino ($-NH_2$) groups of cellulose-g-PAM were protonated, while the COOH groups of cellulose-g-PAA remained intact. Consequently, at pH 1, cellulose-g-PAM was hydrophilic and cellulose-g-PAA was hydrophobic. Therefore, at pH 1, cellulose-g-PAA could reject water and absorb oil. However, at pH 1, water could pass through cellulose-g-PAM, but oil was rejected. But when the pH was raised to 9, the wettability of these cellulose composites changed. The NH_2 groups of cellulose-g-PAM remained neutral at pH 9, but the carboxyl (-COOH) groups of cellulose-g-PAA underwent deprotonation. Because of this, cellulose-g-PAA was hydrophilic and could reject oil at pH 9 while adsorbing water. Due to its hydrophobic properties, cellulose-g-PAM may adsorb oil and reject water at the same pH (pH −9). Their oil/water separation efficiency, which was around 97.6 %, was comparatively high. However, there were certain environmental issues with the cellulose-g-PAM composites' production. For instance, their manufacture required the use of potent chemicals like HNO_3, and the procedure was time-consuming. Consequently, there was a significant chance of secondary environmental pollution.

In another study, Tian et al. [259] developed lysine (Lys) molecularly grafted cellulose porous foams that respond to pH and used them as adsorbents to remove anionic and cationic dyes from wastewater by adsorptive means. The cellulose matrix of the porous form contains

glycidyl methacrylate (GMA) units that give it its pH responsiveness because of the presence of carboxyl (-COOH) and amino (-NH_2) groups. The resulting composite, Cell-g-**PGMA**-Lys, has comparatively high adsorption capacities for both cationic MB and anionic reactive brilliant red X-3B, which were 1210.7 mg/g and 1077.9 mg/g, respectively. The main causes of adsorption between the dyes and the cellulose composite were electrostatic interactions, hydrogen bonds, and hydrophobic interactions. The cellulose structure was given additional functional moieties by the presence of the pH-responsive GMA, which enabled the development of hydrogen bonds and electrostatic interactions with the dyes. This significantly increased the smart cellulose composites' comparatively high dye absorption capability. The amphoteric Cell-g-PGMA-Lys foam's zero-point charge (pHzpc), according to experimental findings, was about 6. At pH levels lower than its pHzpc, the Cell-g-PGMA-Lys foam behaved as a cationic adsorbent and would absorb anionic brilliant red X-3B. When the medium's pH was greater than its pHzpc, on the other hand, it behaved as an anionic adsorbent and formed potent electrostatic contacts with cationic methylene blue dye. After six cycles of adsorption-desorption, Cell-g-PGMA-Lys adsorbent foam still had an 86.9 % and 92.5 % adsorption capacity for brilliant red X-3B and methylene blue, respectively. This was demonstrated by regeneration studies. Thus, environmentally friendly and recyclable pH-responsive cellulose composites are effective adsorbents for both cationic and anionic dyes.

7. Conclusions and future trends

This paper provides a brief overview of several CD, including CA, cellulose triacetate, CMC with a focus on hydrogel's, cellulose/nanoparticles composites, CNCs, CNFs, and CNPs. Additionally, this paper highlights several cellulose processing techniques, such as spinning, mechanical, biological, and chemical approaches. The spinning methods included electro-spinning, dry spinning, wet spinning, hybrid dry jet-wet spinning and solution blow spinning. The cellulose-based materials including adsorbents, membranes and aerogel's added important role for the WW treatment [260]. The kinetics, thermodynamics and sorption isotherm studies of adsorbents and mechanism of adsorption are critically discussed [261]. Effective cellulose-based membrane adsorbents are effective for eradicating pollutants from industrial wastewater, such as colors, dyes, and heavy metal ions. Nano-cellulose is employed to fabricate the membranes including reverse membranes, microfiltration membranes, and forward osmosis membranes which can be used in WW treatment. It has been shown that cellulose -based absorbents are effective at removing oil-based contaminants from water. In addition, CNCs served as fillers and binding agents in the membrane to filter out different pollutants. Dyes, clay particles, heavy metal ions, and biomass microorganisms can all be flocculated by cellulosed-based flocculants. Additionally, they can be employed as disinfectant supports and catalysts to remediate organic and pathogenic water contaminants. The use of CD for water purification is a potential area of research [262]. Resolving the issue pertaining to the separation and flexibility of CNCs for application in industrial wastewater treatment operations will have application in the coming days. This review concluded that, because of their excellent qualities, nano-cellulosic materials have demonstrated extremely significant improvements in water purification applications. As was previously mentioned, cellulose is among the most widely available, nontoxic, biodegradable, and biocompatible materials for the adsorption of contaminants from water bodies [263]. When compared to other materials, the manufacture of cellulose is significantly less expensive due to its relatively large abundance of features and its flexibility in converting into derivatives like nano-cellulose and composites. Since CNPs have numerous future uses, including as nano-photocatalysts, nanomotors, nano-adsorption, nano-membranes, and nano-sorbent for water treatment applications, which can be frequently employed in the water purification system [264]. Other water treatment options, such as desalination with conversion of seawater into drinking water is the target research in future [168,169,261]. Because of the low conductivity of cellulose, electrochemical methods were applied to a very limited extent. However, the formation of new functional groups inside cellulose may improve its electric characteristics, allowing for great electrochemical performance in WW treatment.

CRediT authorship contribution statement

Ramesh Sharma: Conceptualization, Data curation, Formal analysis, Methodology, Software, Writing – original draft. **Pinku Chandra Nath:** Conceptualization, Data curation, Formal analysis, Methodology, Software, Writing – original draft. **Yugal Kishore Mohanta:** Conceptualization, Data curation, Formal analysis, Methodology, Software, Writing – original draft. **Biswanath Bhunia:** Formal analysis, Software, Visualization, Writing – review & editing. **Bishwambhar Mishra:** Formal analysis, Software, Writing – review & editing. **Minaxi Sharma:** Software, Writing – review & editing. **Shweta Suri:** Writing – review & editing. **Maharshi Bhaswant:** Writing – review & editing. **Prakash Kumar Nayak:** Conceptualization, Formal analysis, Resources, Software, Supervision, Visualization, Methodology, Writing - review & editing. **Kandi Sridhar:** Conceptualization, Formal analysis, Methodology, Software, Supervision, Visualization, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Essential oils-based nano-emulsion system for food safety and preservation: Current status and future prospects

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ABSTRACT

The growing public desire for healthy eating has prompted researchers to develop newer methods for incorporating less processed foods without using preservatives in daily diet. Edible coatings based on emulsions contrived from constituents of essential oils (EOs) are thought to be a good way of improving the quality of food in a variety of ways. Nanoemulsion compositions with active ingredients can be utilized to create biodegradable coatings and packaging films that improve functional qualities of the food, its nutritional value, and shelf life. Various studies have scrutinized the deployment of essential oil-based nanoemulsion formulations for efficient food processing and enhancing the distribution of active substances such as colorants, flavoring agents, nutraceuticals, preservatives, and antibacterial agents in foods. Safety considerations such as ingredient security, allergen concerns, proper storage conditions, and compatibility with the food matrix must be carefully considered while utilizing nanoemulsions for food preservation. Herein, current breakthroughs in the use of nano-emulsion-based edible coatings are deliberated as carriers of functional elements such as antibacterial agents, antioxidants, and texture boosters for the retention of the product safety of fruit and vegetables. Besides discussion on the synthesis and evaluation of essential oil-based nanoemulsions, the strategy emphasizes using bioactive components as a replacement for synthetic agents in food preservation.

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1. Introduction

In recent years, the usage of essential oils in nano-emulsion systems has emerged as a promising frontier in food safety and preservation. Essential oils have garnered recognition for their natural antimicrobial properties and capability to combat foodborne pathogens as the global food industry continuously seeks innovative strategies to increase the shelf life of perishable products while ensuring consumer health (Maurya et al., 2021b; da Silva et al., 2022; Omar et al., 2022). This innovative strategy of combining essential oils with nano-emulsions has the potential to revolutionize food preservation techniques. Currently, there's been tremendous progress achieved in the marketplace for healthier dietary alternatives, like enhanced consumption of freshly cut fruits and vegetables. Users evaluate and gravitate to the next most agreeable elements among all these items, namely originality, nutritious qualities, flavoring, and innovative tastes that maintain the aesthetic over extended time periods (Bodirsky et al., 2020; Jadhav et al., 2021).

Essential oils, which are produced from plant sources, exhibit significant antibacterial and antioxidant characteristics. However, the utilization of these compounds in the field of food preservation has been constrained as a result of their inadequate solubility in aqueous solutions (He et al., 2020; Álvarez-Martínez et al., 2021). The difficulty is effectively addressed by nano-emulsion technology, which involves the reduction of oil droplets to nanoscale dimensions. This process enhances the solubility of the oil droplets and facilitates their dispersion in aqueous solutions (Suhag et al., 2020; Yaashikaa et al., 2023). Essential oils possess bioactive constituents that have the capacity to impede the proliferation of harmful microorganisms, encompassing bacteria, fungus, and viruses, within food items (Tripathi et al., 2021). Nano-emulsions have been found to augment the antibacterial effectiveness of essential oils by the amplification of their surface area and subsequent interaction with foodborne microorganisms. The aforementioned findings carry substantial ramifications in the realm of food safety, as well as in the mitigation of foodborne infections (Mushtaq et al., 2023; Zhang et al., 2023). These coatings and films perform specific functions such as moisture retention, oxygen absorption, and element leakage mitigation besides serving as aids in the preservation of food's nutritional value and its external characteristics (Blancas-Benitez et al., 2022). The nature of coatings can be selected based on the ingredients in the food and their intended use, as edible coatings offer certain unique uses and significant benefits in preventing deterioration in quality (Nunes et al., 2023).

In terms of active ingredients, essential oils along with additional extracts from plants have been considered in the fabrication of edible coatings due to their proven ability to prevent microbial growth, which harms the products and shortens their duration of storage. Such coatings can also capture free radicals, slow down degradation, and arrest oxidative damage occurrences by utilizing the antioxidant properties of herbal extracts and essential oils (Mushtaq et al., 2023). Today, the development of transporters that carry certain active compounds, like polyphenols and carotenoids, with antibacterial and antioxidant capabilities, offer promising option for nanotechnology. With no negative impacts on human health or the natural world, the preservation of food and packing is now achievable by virtue of the development of nanotechnology in the culinary and farming sectors (De Bruno et al., 2023). It is envisioned that in not-too-distant future, engineered containerization will be substituted with edible coatings as they are considered a superior alternative in combating quality degradation; they meet all the prerequisites such as decay safeguarding, high-quality upkeep, conserving, longevity implications, eco-friendliness, and economical practicality (Suput et al., 2015). Once the tender fruit gets sliced, it becomes highly susceptible to decomposition as the slicing affects the inner cells of the fruit's flesh resulting in pathological exertion (González-Aguilar et al., 2009).

The growing inclination of consumers towards natural and clean-label components has led to a corresponding demand for essential oil-based nano-emulsions, which are in line with this prevailing trend. They provide a natural substitute for synthetic preservatives, which are frequently regarded as less preferable by consumers who prioritize their health. This has the potential to facilitate the advancement of food items that are both safer and more commercially viable (Zamuz et al., 2021). Nano-emulsions have been demonstrated to be highly successful in inhibiting the oxidation process of lipids and proteins in food, thereby leading to a significant extension of the products' shelf-life. This is especially advantageous for perishable commodities such as oils, dairy goods, and meat, as they are prone to spoiling and rancidity. Despite the potential that essential oil-based nano-emulsions hold, there exist certain limitations pertaining to their formulation and stability (Raghav et al., 2016; Bodirsky et al., 2020; Jadhav et al., 2021). The stability of these systems can be influenced by various factors such as pH, temperature, and the selection of emulsifiers. In order to maintain consistent performance in practical settings, it is imperative for researchers and food technologists to confront and tackle these challenges. As the advancement of this technology progresses, regulatory agencies are applying greater scrutiny to nano-emulsions derived from essential oils (Ravera et al., 2021). The legislation and labeling requirements pertaining to food safety are undergoing continuous development. It is imperative for the food businesses to adhere to these standards, while simultaneously providing evidence of the safety and effectiveness of their goods. The potential of essential oil-based nano-emulsions in the realm of food safety and preservation shows considerable promise. Current research endeavors are aimed to optimize formulations, improve stability, and investigate innovative sources of essential oils. Furthermore, the establishment of partnerships among scientists, food producers, and regulatory authorities will play a pivotal role in the progression of this discipline (Campolo et al., 2020; Taban et al., 2020; Zamuz et al., 2021; Mushtaq et al., 2023).

This review's main objective is to acknowledge, assess, and assign the remarkable impact of botanical extracts (Essential Oil; EO) on the shelf life of food in multiple variations, like immediate absorption in films that are edible or through the use of nanoemulsions. Throughout this paper, the essential oils' most recent advancements, advantages, and function as an edible coating for food products have been comprehensively discussed with emphasis on significance, purposes, formulation techniques, impacts on longevity, various functional attributes, and possible futures of edible coatings. Fig. 1 highlightes the aspects of preservation and extension of food shelf-life by essential oil-based nanoemulsions.

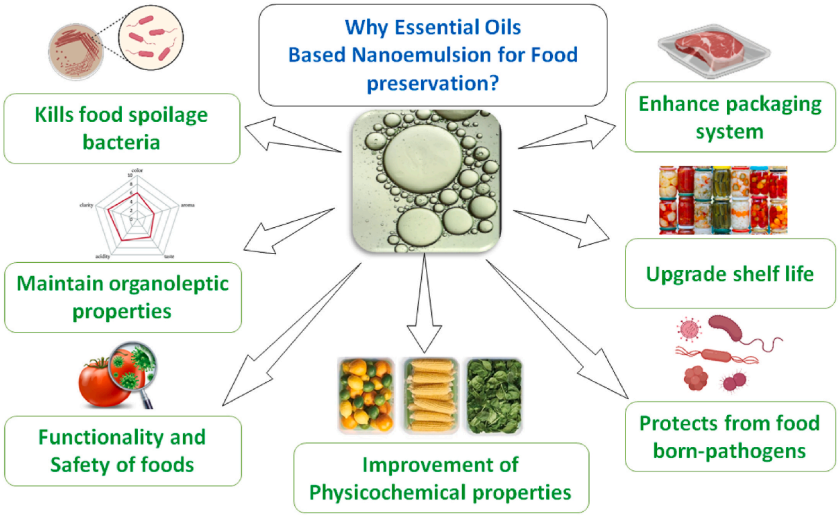

Fig. 1. Potential of essential oils-based nano emulsion system in food preservation and shelf-life enhancement.

2. Formulation and characterization of nanoemulsions

Nanoemulsions comprise colloidal dispersions of droplets of oil containing tiny fragments (usually 10–200 nm in dimension) in an aqueous solution. Nanoemulsions, in contrast to clear, opaque, and thermally stable microemulsions, are merely stable under kinetic conditions; nanoemulsification concept is centred on emerging nanotechnologies that have the potential to transform the food sector. The prolonged mechanical durability of a nanoemulsion (with no evident flotation or agglomeration) is also referred to as "approaching thermal stabilization." (Chen and Hu, 2020). The contemporary culinary sector's prevailing pattern has been to create foods with functional properties that are expressly intended to improve the well-being and health of people. Polyunsaturated fats, vitamins that are soluble in oil, phytosterols, curcumin, carotenoids, and flavonoids are among the most common physiologically functional components (McClements, 2015). Many hurdles need to be circumvented prior to the addition of various lipophilic metabolites to conventional meals, like poor water solubility, the formation of crystals, biochemical unpredictability, limited duration of action, and constrained effectiveness (Iversen et al., 2022). Nanoemulsification can be accomplished through a couple of methodologies, namely high-energy and low-energy emulsification. It can be employed in the production and distribution of wholesome foodstuffs to boost the dissolution and accessibility, promote potency of substances, retain sensory attributes, and manage nutraceutical emissions (Huang et al., 2019). Various methods for the preparation of nanoemulsion are illustrated in Fig. 2.

2.1. High energy approaches

Mechanical instruments are deployed in high-energy techniques that generate powerful forces of destruction capable of breaking and mixing the water and oil components and converting them to microscopic oily particles. It is a widely prevalent procedure that employs high-pressure valve homogenizers, microfluidizers, and ultrasonic homogenizers (S and Kumar, 2022). High-energy tech-

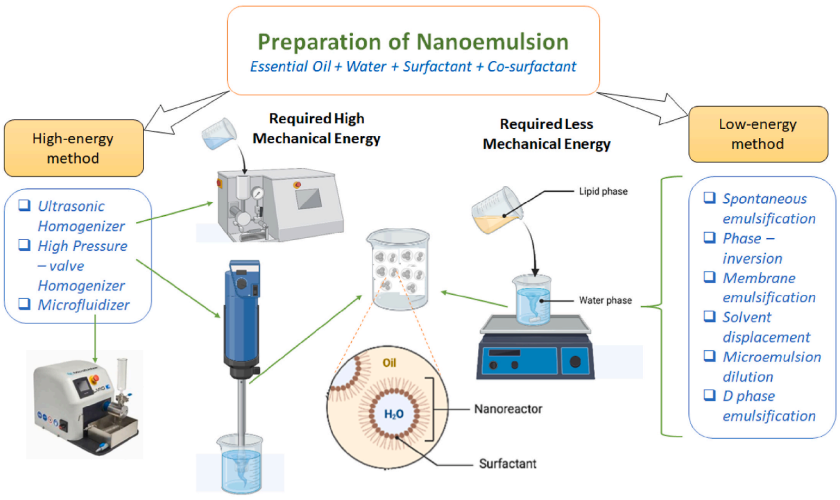

Fig. 2. Conventional methods employed for preparing the nanoemulsions.

nologies can be utilized to generate nanoemulsions on an extensive basis as well as for creating them from a variety of ingredients. These methods have emerged as the main technique for creating nanoemulsions across the food manufacturing business (Alliod et al., 2019).

2.1.1. High pressure – valve homogenizer

High-pressure valve homogenizers are among the most frequently utilized machines in the culinary business which generate standard droplet-size emulsions. These instruments are significantly better at minimizing the size of droplets prior to crude aggregation rather than rapidly arranged formulations using a pair of immiscible liquids. In essence, the crude emulsion is created using a high-shear blender before it passes through a homogenizer. Upon its way back, a homogenizer pump drives the grainy emulsion into its chamber, and its forward movement drives it out via an intricate nozzle at its terminus. The emulsion is subjected to significant damaging factors, including turbulent motion, shear forces, cavitation, smashing, shear strain, pressure gradient, and tangential shearing, as it travels along the valve, causing the fragmentation of bigger droppings into tiny particles. The higher the homogenization tension, the more quickly the emulsifier adsorbs, while at the lower surface tension, ensued droplet sizes are tinier (Levy et al., 2021). Despite this, particles having dimensions of less than 100 nm are feasible under specific circumstances such as, excessive emulsifier concentration, minimal surface tension, and adequate viscoelasticity. However, the instrument's power emits heat waves, leading to decreased effectiveness. In contrast to alternative high-energy approaches, these types of instruments do not offer effective droplet dimension variance (Peng et al., 2019).

2.1.2. Microfluidizer

A microfluidizer akin to a high-pressure homogenizer uses high pressure to force the emulsion to mix through tiny passageways to help break up the droplets. It is frequently deployed in the pharmaceutical sector to create emulsions, as well as in the beverage and food sectors to make flavoring and nutritive emulsions, and homogenous milk. The microfluidization concept is to split the emulsion passing down an aperture into a pair of flows, thus allowing each of them to travel through a distinct, appropriate canal, and subsequently lead both of them to come into contact with one another in a mixing tank (Li et al., 2022). The ensuing streams subsequently tumble against one another in a mixing room, creating a powerful, destructive impact that breaks apart the particles into microscopic emulsions. Extremely tiny fragments (droplets) having dimensions in the sub-micron range can be created as the blend passes through these microchannels and into the area of impact. In the microfluidization technique, homogenous stress develops, and emulsifier percentages are favourably associated with the droplet size, whereas the percentage of viscous amount of the scattered phase to the constant phase is inversely related (Santos et al., 2016). The amalgamation of a greater maximal rate of shear, a substantial amount of nano-droplet fluctuation, and a slightly regular distribution of sizing are the key benefits of microfluidizers. Nevertheless, microfluidizers are quite expensive, and the procedure's effectiveness suffers as a result of their significant tendency to wear out (Gulzar and Benjakul, 2020).

2.1.3. Ultrasonic homogenizer

The ultrasonic approach uses high-intensity ultrasonic energies that have a frequency above 20 kHz to generate the powerful force of destruction necessary for tearing out both water and oil into extremely small particles. The fundamental concept of phacoemulsification is explained by a pair of mechanisms: the first is the generation of link vibrations by the application of third-party noise fields and the dispersion of the oil phase as particles in the perpetual phase; the subsequent one is the phenomenon of cavitation via the application of ultrasonic waves. Simple acoustic impulses' stress induces the development and breakup of microbubbles as well as a remarkably parallel, intensely concentrated Swiss circulation that fragments the main droplets into particles that are less than one micron in dimension (Chen et al., 2022). The solution loops across the high-power zone concurrently because of the ambiguity of the generated sounds, causing all the droplets to suffer excessive shear force. In essence, the production of emulsion droplets occurs because of the intense waves of shock that ultrasonic homogenizers trigger in the fluid that circulates around them. Nonetheless, the technique is currently being assessed to determine whether it will work well for commercial uses (Ghosh et al., 2013).

2.2. Low energy approaches

The fundamental idea behind low-energy nanoemulsion production is that as the atmosphere or the chemistry of an oil-water blend alters, oil droplets naturally emerge. The chemical and physical characteristics of the oils and co-surfactants, as well as alterations in surface tension across transitions between stages, all play a major role in the creation of the appropriate-sized nanoemulsion particles (Safaya and Rotliwala, 2020). Minimal production expenses, an easy technique for fabrication, and the capability to achieve fine dimensions of particles are salient advantages of low-energy processes (Baig et al., 2021). The fundamental drawback of these methods is their extremely poor manufacturing output, despite their ability to use an extensive selection of oils and emulsifiers. Spontaneous emulsification, phase inversion temperature (PIT) emulsification, phase conversion synthesis, and the emulsification point method are among several of the widely utilized techniques (Dey et al., 2018).

2.2.1. Spontaneous emulsification

When nonpolar oil, water-friendly surfactant, and hydrophilic organic solvent are combined with surfactants in an organic phase, either in water or organic substance comprising inert oil, hydrophilic organic solvent, and surfactants, nanoemulsions are created (Yildirim et al., 2017). Self-emulsification is the process of creating nanoemulsions by allowing particles of the surfactant and/or solvent to migrate from the dispersed state to the continuous state without forcing the surfactant to spontaneously alter how it bends (Su and Zhong, 2016). To create a nanoemulsion during the emulsification process, a fairly significant amount of chemical-based deter-

gent is needed. Consequently, the natural emulsification approach is unlikely to be extensively used in the food sector due to solvent elimination, enforcement, involved expenses, or sensory considerations (Choi and McClements, 2020).

2.2.2. Phase – inversion method

The inverted phase technique is exploited to switch between an Oil suspended in Water (O/W) emulsion and a Water suspended in Oil (W/O) emulsion alternately in response to variations in particular parameters. Two processes comprise the phase inversion technology: the phase inversion temperature (PIT) and the phase inversion composition (PIC). PIT is both a specific temperature that determines the dissolution of the emulsifier in the oil and water phases and the temperature at which an O/W emulsion transforms into a W/O emulsion (or vice versa) (Ren et al., 2019). The PIT approach may be employed to create nanoemulsions that naturally develop by altering the temperature-time pattern of specific combinations of oil, water, and non-ionic surfactants (Sadeq, 2020). The PIC technique modifies the overall formulation to alter the surfactant's ideal geometry. The phase-inversion approach offers the benefits of being easy to use, resistant to degradation of drugs during the preparation, minimal use of energy, and commercial production (Feng et al., 2020).

2.2.3. Membrane emulsification technique

The approach of spot emulsification using membranes with pores, known as the membrane emulsification process, was invented in Japan. Over the past 25 years, membrane emulsification has drawn ever more interest as a substitute technique for creating emulsion. The basic idea behind this process is to forcefully transfer the dispersed state through the holes of a microporous film into the continuous phase; gradual action is responsible for the creation and division of emulsified drops at the brink of the apertures. Either an absolute liquid or an emulsion might be the phase that is dispersed as droplets (Vladisavljević, 2019). Simple emulsions, including droplets of oil in water (O/W) or water in oil (W/O), can be produced by using either immiscible solvent as the continuous phase (Laouini et al., 2012). This technique can also be used to create dual or numerous emulsions, which include water-in-oil-in-water (W/O/W) and oil-in-water-in-oil (O/W/O) emulsions. The membrane emulsification technology designed to create nanoemulsions offers several advantages over other emulsification methods, including minimal energy usage, tunable particle dimension, unidirectional dispersion, good entrapment velocity, etc (Gehrmann and Bunjes, 2016). It also requires no shear or heat deterioration and deploys fewer detergents and has tighter particle dispersion than high-energy procedures. The primary drawback of this technique is that it is challenging to improve the output due to the poor flow of the dispersed state across the membrane (Alliod et al., 2019).

2.2.4. Solvent displacement method

A water-soluble organic solvent that contains a lipophilic essential component is mixed with an emulsifier-containing aqueous phase to create the solvent displacement technique. In this method, the organic solvent dissipates rapidly through the aqueous phase and can create a nanoemulsion with a significant degree of encapsulation (Pineda-Reyes et al., 2021). At lowered pressure, the deployed organic solvent in the manufacturing process can be extracted from the nanoemulsion. This method's restriction to water-miscible solvents is a major drawback (Trimaille et al., 2001), however.

2.2.5. Microemulsion dilution

This procedure which is simple to scale up is also referred to as the self-emulsification process. The dilution technique is used to create the nanoemulsion at an ambient temperature. Swiftly adding significant amounts of water dilutes the oil-in-water microemulsion, thus minimizing the level of surfactant necessary for retaining its thermodynamic equilibrium (Vladisavljević, 2019). Due to the constant temperature and absence of rapid mixing steps, it uses diminutive energy (Feng et al., 2018).

2.2.6. D phase emulsification (DPE)

Like earlier approaches, the D-phase system uses a surfactant, water, and oil, as well as the addition of an alkyl polyol, to create an o/w nanoemulsion. In comparison to other low-energy techniques, the DPE method requires a small amount of surfactant, fails to strictly conform to the hydrophilic-lipophilic scales or correct surfactant combination, doesn't involve solvent, and purportedly uses a lesser amount of energy than the PIC method (Yukuyama et al., 2018).

3. Essential oils (EOs) and their functional ingredients as nanoemulsion

3.1. Essential oils with antimicrobial properties

The potency of EOs and their vital constituents over a variety of yeast, bacteria, and molds has been frequently mentioned and is determined to be influenced by EO substance profile and architecture, as well as the sort and form of intended microbes (Mahdi et al., 2021a; Kalagatur et al., 2018). The antimicrobial efficacy of EOs does not rely on any particular process, and the effect varies depending on the constituents of the essential oil. Membrane disruption is the most prevalent route of antibacterial action (Pateiro et al., 2021). Target sites of essential oil based nanoemulsion and its mode of action has been illustrated in Fig. 3.

Mustard EO outperforms cinnamon EO in terms of antibacterial (EOs destroy the bacterial colonies) or bacteriostatic (EOs impede bacterial growth, allowing microbial cells to recover normal reproductive capabilities). This is possibly accounted for by the disparities in the behavior of two EOs (Falleh et al., 2020). EOs are known to breach membranes and destroy the endomembrane network of yeast cells and mold growth. Furthermore, EOs have been shown to interfere with biofilm's three-dimensional organization by lowering extrinsic polymer molecules, to hinder biofilm metabolic processes and oxygen consumption, and to have detrimental impacts on the mitochondria (Hu et al., 2019). According to the majority of investigations, EOs are marginally better at working over gram-positive microbes relative to microbes that are gram-negative (Vidács et al., 2018). The existence of a lipophilic tail of a compound

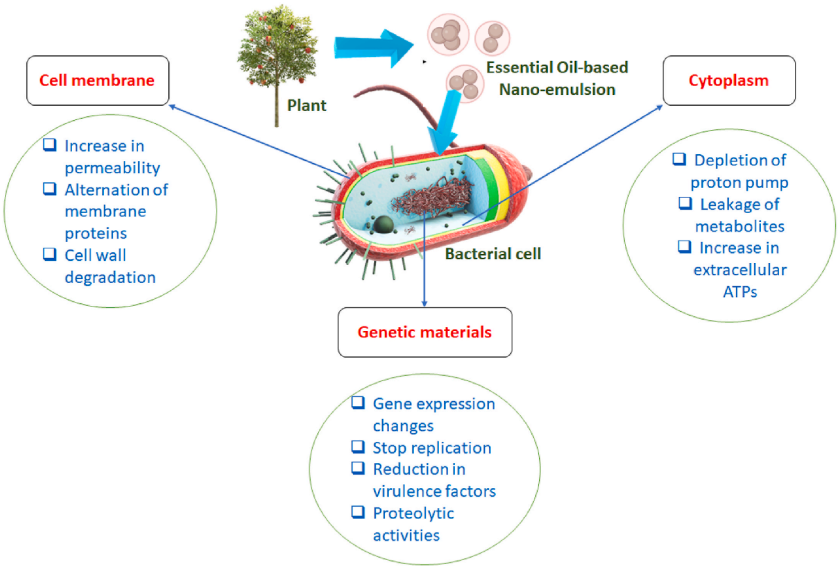

Fig. 3. Modes of antimicrobial action of essential oil based nanoemulsion.

called lipoteichoic acid in gram-positive microorganism's cellular membranes render them extra vulnerable to EO infiltration (Chouhan et al., 2017). Furthermore, gram-negative microorganisms are particularly impervious to the effect of EOs owing to their sturdy construction and complicated outer coating abundant in lipopolysaccharides, which acts as a shield and prevents hydrophobic molecules from penetrating (Bazargani and Rohloff, 2016). According to some investigations, gram-negative microorganisms are less immune to EOs compared to gram-positive microorganisms. Gram-negative microbes, like *Acinetobacter baumannii* and *Vibrio parahaemolyticus*, have been shown to be the most responsive to EO from *Eucalyptus camaldulensis Dehnh.* (Ksouda et al., 2019). Numerous EOs and associated phenolic derivatives have been associated to the adhesion and destabilization of microbial membranes. Because of their lipophilic nature, EOs and their vital constituents have been shown to rapidly permeate and concentrate in the lipid double layer of intracellular membranes. They bind to the fatty acid groups of cell membranes, triggering disruption and deterioration of the membrane's various sections via suppression of enzymatic processes or loss of the electron transport system (Bouyahya et al., 2019). As a result, the sturdiness of the phospholipid bilayer is compromised, and its ability to leak surges. The increased permeation facilitates antimicrobial substance infiltration, disturbs the normal functioning of cells, and ends up in the escape of indispensable intracellular constituents (ions, proteins, and nucleic acids), an impairment of the proton motive force (PMF), a decrease in the potential of the membrane, and an exhaustion of adenosine triphosphate (ATP) (PATHANIA et al., 2018). To some extent, the elimination of intracellular components may be endured with no interruption of survivability. The longer the contact period among EOs and bacteria, nevertheless, the greater the decline of intracellular content, which causes the death of cells via necrotic or apoptotic pathways (Ju et al., 2019). The EOs of *Amomum villosum* Lour and *Origanum compactum* Benth. caused a spillage of macromolecular particles like RNA, proteins, and DNA in methicillin-resistant *S. aureus* (MRSA), *E. coli*, and *B. subtilis* (Bouyahya et al., 2019; Tang et al., 2020). Upon exposure to carvacrol and thymol, crucial cytoplasmic elements, which include charged particles and protein complexes, have also been observed emanating from *S. enteritidis* and *E. coli* (Yammine et al., 2023). Furthermore, recent investigations have uncovered that those sub-inhibitory doses of citral and *Thymus vulgaris* L. EOs enhanced sub-lethally wounded Listeria and Salmonella microbial cell walls (Ed-Dra et al., 2021). EOs and their active constituents have been shown to disrupt the QS association process by binding to the receptors of bacterial cell walls, diminishing signaling molecular recognition, destroying communication between cells, and ultimately inhibiting the growth of biofilm (Maurya et al., 2021a). In L. *monocytogenes* biofilms, epigallocatechin gallate, a polyphenol present in tea extracts, has been discovered to negatively govern a quorum sensing gene, the accessory gene regulator A (agrA). Cinnamaldehydes, which are understood to have the most antibacterial effect, have been found in many studies to bind to the filamenting temperature-sensitive mutant Z (FtsZ) cell division regulatory protein, thus suppressing cell division (Du et al., 2018).

3.2. Essential oils in different edible coatings

Essential oils have immense potential for use in the protection of food, storage, and packing. The use of essential oils and gelatin in coatings can have an antibacterial effect as well as an enhanced physical and chemical contribution. In cases where essential oil is mixed with chitosan, its qualities are enhanced. The combination of EOs with methylcellulose or chitosan-based biodegradable coatings, have significantly boosted their subsequent antimicrobial effectiveness (Kamle et al., 2019). The development of mold and yeast can be efficiently prevented by food-grade coatings infused with a variety of EOs as demonstrated by films made from starch infused with the EO of orange, being significantly beneficial to *S. aureus* and *L. monocytogenes* isolates (do Evangelho et al., 2019). Moreover, the effect of nanoclay film (made by combining sodium gelatin in a solid state with aqueous sodium alginate alongside citrus essential oil in ratios of 0.2% and 0.4%) has been found to be more effective in inhibiting the spread of *Vibrio parahaemolyticus*, *L. monocytogenes*, *S. typhi*, and *Streptococcus iniae* in seafood.

The adherence to food surfaces is critical for the coatings to accomplish their destined objective's goal. Several EOs, such as oregano, cloves, lemon, and many others, have been concocted with a variety of blends and mean droplet dimensions along with surface charge to boost their in vitro effectiveness with food-grade coatings of chitosan along with additional substances, thereby increasing their antimicrobial and antifungal characteristics (de Oliveira Filho et al., 2021). Food-safe coatings extend the life expectancy of fruits and protect them from losses following harvest by reducing metabolism and the elimination of water. Surveyinga specific study, the contemplations turned to compostable edible food packaging for proteins and complex carbohydrates (Huang et al., 2021).

According to presently accumulated knowledge, there is a lot of potential in deploying polysaccharide-based palatable coatings incorporating EOs in view of their excellent antibacterial and antioxidant qualities (Panahirad et al., 2020). Because of their ease of recovery and utilization, chitosan, pectin, alginate, and gellan make up the majority of commonly used polysaccharides employed as food-grade coatings. Furthermore, cereals, vegetables, and fruits are economical sources of the aforesaid polysaccharides (Aguirre-Joya et al., 2018). Starch serves as an inherently degrading and sustainable biopolymer that has been widely deployed owing to its abundant supply and inexpensive price tag. Starch polymers have been utilized in biodegradable platters, manufacturing items, and food-safe encasing and wrapping additionally, cross-linked cassava starch edible coatings, strengthened by nano-crystals of starch, enhanced the longevity of shelf-life of rated Huangguan pears. The outcomes demonstrated that a starch-based edible covering could retain the pristine characteristics of Huangguan pears maintained at 20 °C for a period of thirty days. Mohseni et al. (2020) investigated the physical and chemical characteristics of green-synthesized silver nanoparticles included in synthetic nanostarch-based edible coatings wherein a silver-starch edible coating considerably minimized the shortcomings of the original starch coat and can be used as a potential food wrap.

3.2.1. Aloe vera

One of the naturally occurring formulation that has received a lot of interest lately is aloe vera gel deployed as an antimicrobial layer intermediary. It is mostly composed of polysaccharides that quickly form a homogeneous covering on the exterior of the vegetable or fruit (Hassan et al., 2018). Because of the inclusion of bioactive elements, aloe vera imparts antibacterial properties to fruit coatings and antioxidant benefits to fresh food (Nicolau-Lapeña et al., 2021). Currently, aloe vera gel coating has been combined with basil essential oil to preserve the freshness of strawberries during refrigeration by slowing respiration while minimizing loosening, loss of weight, and the development of fungi (Mohammadi et al., 2021).

(Karunarathna et al., 2021) combined cinnamon EO with aloe vera and tested the regimens' efficacy against mango stem-end rot pathogenic organisms; *Lasiodiplodia theobromae*, *Pestalotiopsis* sp., and *Phomopsis* sp. were effectively restrained from growing as a result of the administration. (Tzortzakis et al., 2019) also improved aloe vera gel coatings by creating sage EO combination to preserve tomato freshness wherein additional discernible quality was attained after harvest benefit than the tomato pretreatment. Furthermore, aloe vera gel has been used with lemongrass EO and evaluated for its application on the outermost layer of strawberries (Hassan et al., 2022). Coated fruits offered favorable cure outcomes because the coating's application contributed to decreasing the overall microorganisms found in the fruits and enhancing the antioxidant effect of the fruits. Earlier, the inhibitory effect of aloe vera and lemon peel concentrate on *Colletotrichum musae* on a banana has been explored (Jodhani and Nataraj, 2021). To prolong the storage duration of a banana, the covering contributed to minimizing proportional reductions in weight and rot frequency and sustaining key fundamental characteristics of the fruit.

3.2.2. Wax coatings

The use of a food-grade film comprising candelilla wax and powerful antioxidant ellagic acids on fruits was found to inhibit the proliferation and propagation of anthracnose while retaining its luster and nutritional value throughout preservation (Alvarez-Perez et al., 2019). Beeswax was embedded on a cellulose nanofibrils/carboxymethyl chitosan-coated substrate by (Xie et al., 2020). *Staphylococcus aureus* and *Escherichia coli* were inhibited by the homogenized solution's coating with high degree of stability and antibacterial properties. Additionally, because of its superior mechanical and barrier properties, the coating mixture has the capability to retain berry fruits in their natural state for an extended period of time.

(Kowalczyk et al., 2019) developed an innovative carboxymethyl cellulose (CMC)/candelilla wax mixture to evaluate its benefit for the physiology, value, and microbial content of Brussels sprouts. The administered sprout, on the other hand, shows a lack of weight loss, appearance, or amount of water. The covering delayed metabolism, hastened pigment deterioration, and quickened polyphenol oxidase, the results of which influenced the sensory properties of the fruits and vegetables. Because of ethylene accumulation and deficient exchange of gases, the coating damages the specimen by fostering the growth of fungi. (Miranda et al., 2021) utilized carnauba wax nanoemulsions to create *Zingiber officinale* Roscoe (ginger) EO to suppress fungal development on papaya. Not long ago, (Saeed et al., 2021) used the wax of carnauba as a coating substrate with peelings of orange EO to protect strawberries from *Penicillium expansum*; EO could reduce up to 96% of fungal growth following its preservation. (Valle-Ortiz et al., 2019) added thyme (*Thymus vulgaris* L.) EO to a candelilla wax and chitosan-coated solution to inhibit the development of microbes on cactus pear and improved the longevity of the fruit.

3.2.3. Natural gum

Bacterial pathogens are commonly detected in vegetables and fruit. Gum arabic, as illustration, has demonstrated promising antibacterial effectiveness over infectious molds embracing *Penicillium digitatum*, *Colletotrichum gloeosporioides*, and *Geotrichum citriaurantii*. Gum arabic and starch from maize are used to cover pomegranate fruits along with refrigeration. The protective layer significantly reduced the degradation in contrast to exposed pomegranate specimens (Huang et al., 2021; Kawhena et al., 2021). Additional investigations have demonstrated that, when used as packaging supplies, gum arabic is effective at thwarting the development of fun-

gal organisms in perishable foods like guavas, mangoes, strawberries, and tomatoes (Daisy et al., 2020; El-Gioushy et al., 2022). On the other hand employed food-grade coatings such as gum arabic to increase the product longevity of persimmon fruit maintained at ambient temperatures, (Saleem et al., 2020). In administered specimens, decreased body weight, H_2O_2, malondialdehyde content, and leakage from the membrane have all been mitigated. Gum arabic has been demonstrated to inhibit the metabolism of enzymes like cellulase, polygalacturonase, and pectin methylesterase, while promoting the function of peroxidase, ascorbate peroxidase, catalase, and superoxide dismutase. The adjusted pH, ascorbic acid, total phenolics, and antioxidant properties of the administered persimmons were all higher. (Alamri et al., 2020) came up with a novel encasing composition comprised of arabic gum that was enhanced by mint and thyme EO to improve the quality of peaches after harvest. The unique encasing compositions safely and profitably hindered the growth of fungi (*Botrytis cinerea*, *Rhizopus stolonifer*, and *Penicillium expansum*) and limited the deterioration throughout the preservation phase of the fruit. (Iftikhar et al., 2022) used lemon peel EO encapsulated in guar gum and a chitosan-based coating mixture to enhance the storage life of pear; coated pear specimens lost a lesser amount of mass and exhibited superior firmness in the fruit over uncovered fruit allotments.

3.3. Essential oils on sensory attributes of foods

Based on their sole fundamental applicability or through blends of other preserving aspects, EOs have the capability to play an integral part in microbiological tranquility and security with constant maintenance of the dietary value. The elemental composition of EOs causes their distinct scents and qualities. To varying degrees, each element determines the ultimate trait. For a long time, EOs have been used as additives in foods, mostly as fragrances and flavors, in addition to being useful components (Mariod, 2016). Food-borne bacteria could be unlikely to overcome the blockades formed by EOs in disinfected foodstuffs, resulting in their deterioration; this barrier is designed to enhance the tasting qualities and microbiological durability of meals. In furtherance of nanoencapsulation, various microencapsulation investigations of EOs have been conducted (Granata et al., 2018). The structural and sensory features of Jujube (*Ziziphus jujuba* Mill) fruit were improved by encapsulating *Zingiber officinale* (ginger) EO with chitosan and sodium carboxymethyl cellulose. Following a week of storage, profound blackspots were found on the exterior of uncovered jujube fruits; nonetheless, no rotting appeared in jujube fruit specimens containing microencapsulated EOs. The tenderness and sensory qualities of jujube fruits were evaluated using the red and decay indexes wherein it was uncovered that EO microencapsulated fruits exhibited higher sensory quality features in terms of physical attributes such as crunchiness, stiffness, and juiciness (Ban et al., 2020). A further investigation found that the maturation of Syringe EO microencapsulated (SEOM) *Prunus persica* (L.) Stokes fruit was slowed. Moreover, throughout the preservation time, the generation of ethylene was inferior to that of the control group. SEOM treatment increased the peach-like fragrance and decreased the grass-like odor, primarily in the final stage of preservation, safeguarding the peach scent under refrigeration (Yang et al., 2019). *Origanum majorana* L. essential oil encapsulated in chitosan nanoemulsion caused in situ inhibition of lipid peroxidation and aflatoxin B_1 (AFB_1) production in maize without altering their sensory properties (Chaudhari et al., 2020). Likewise, chitosan nanoparticles containing *Heracleum persicum* fruit EO had no deleterious effects. It was, however, more beneficial in postponing red bell pepper sensory degradation (Taheri et al., 2020). Chitosan nanoparticles combined with microencapsulated *Eryngium campestre* L. EO exhibited no negative impact on the flavor of fresh cherry fruits (Arabpoor et al., 2021). Such coating boosted sample stiffness while preserving color and overall carotenoid amount and reducing weight loss. Furthermore, food products with encapsulated EOs perform more effectively than foods receiving pure oil administration. When executing sensory evaluations of EOs used in food systems, acceptable sensory acceptability has been invariably reported, albeit with distinctive odor and flavor. Encapsulated EOs boost the antimicrobial activity at minimal levels without substantially changing the sensory properties of the products (Kraśniewska et al., 2020; Ksouda et al., 2019) employed sodium alginate to create an edible coating enhanced with *Pimpinella saxifraga* L. EO (PSEO) for coating on fresh Beja Sicilian cheese. Loss of weight, acidity, activity of water, color, free radical and microbiological stability, and sensory properties were all assessed. In terms of sensory evaluation, cheese samples coated with PSEO-loaded sheets have been demonstrated to be superior over uncovered specimens on the basis of criteria like odor, color, and flavor. Chitosan and tripolyphosphate were utilized as vehicles for encapsulating Moringa essential oil (MO) in nanoparticles, which were subsequently electrospun into nanofibers to serve as active packaging material for Cheddar cheese. This is pertinent to highlight that the visual data and sensory characteristics of the cheese specimens administered by the nanofibers stood robust throughout retention, suggesting that Moringa oil/chitosan nanoparticle-embedded gelatin nanofibers have an excellent prospect to serve as cheese preservers (Lin et al., 2019). A summary of several common Eos, their source of extraction, functional compounds and their primary incidence is mentioned in Table 1.

4. Advantages of nanoemulsions in food system

There has been quite a lot of speculation about using nanotechnology-based innovative techniques to enhance the benchmarks for foodstuffs, usage of nanoemulsions in the food-related collateral sector being one of the key prospects. Significantly, microbial development and deterioration are two variables that affect the freshness and preservation of foodstuffs, vegetables, and fruits. According to the application, nanoemulsion-based methods of administration may additionally encompass pigments, seasonings, preservers, disinfecting substances, or nourishments. When contrasted with specimens of standard protocols, this approach can forestall microbial development, variations in food color and physical attributes, decreasing weight, water retention diminution, bad sensation, and aesthetics, and also reduce the extent of decomposition and discoloration (Ahari and Naeimabadi, 2021).

Table 1
– Source, Primary incidence, functional group, and advantages of several common Essential Oil.

Essential Oil	Source of EO	Primary incidence	Functional Compounds	Advantageous consequences	References
Anise (*Pimpinella anisum* L.)	Seeds	East Mediterranean region and India	*trans*- Anethole (phenylproprenoid), Estragole (phenylpropanoid), γ-Himachalene (sesquiterpene), Linalool (oxygenated monoterpene), Camphor (oxygenated monoterpene).	Insecticidal effect against *Culex quinquefasciatus*, anti-inflammatory activity on bronchial and tracheal epithelial cells in the respiratory system	Iannarelli et al. (2018)
Basil (*Ocimum basilicum* L.)	Leaf and Flower	India	Estragole (phenylpropanoid), Linalool (oxygenated monoterpene), Eugenol (monoterpene hydrocarbon).	Enhances mortality of *Culex quinquefasciatus*, antibacterial activity against *Escherichia coli.*	Sundararajan et al. (2018)
Cinnamon (*Cinnamomum verum* J. Presl)	Leaves and bark	Sri Lanka and Malabar coast of India	Cinnamaldehyde (aldehyde), Eugenol (monoterpene hydrocarbon), β-Caryophyllene (sesquiterpene hydrocarbon), Cinnamyl acetate (ester), Cinnamic acid (carboxylic acid), Linalool (oxygenated monoterpene), Benzyl Benzoate (ester).	Antibacterial activity against *Escherichia coli, Agrobacterium tumefaciens*, acaricidal activity against the ticks *Haemaphysalis longicornis, Rhipicephalus microplus*.	Singh et al. (2017)
Clove (*Syzygium aromaticum* (L.) Merr. & L.M. Perry)	Flower, stem, bud, leaf	Indonesia	Eugenol (monoterpene hydrocarbon).β-Caryophyllene (sesquiterpene hydrocarbon), α- Caryophyllene (sesquiterpene hydrocarbon),	Leishmanicidal effects on promastigotes of *Leishmania tropica* and *Leishmania major*, good in-vitro antioxidant, antibacterial activity against *Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa* and *Klebsiella pneumoniae*.	Mohammadi et al. (2021)
Cumin (*Cuminum cyminum* L.)	Seed	Eastern Mediterranean region and India	Cumin aldehyde, Cumin alcohol, γ-Terpinene (monoterpene hydrocarbon), p-Cymene (monoterpene hydrocarbon), β- Pinene (monoterpene hydrocarbon).	Antioxidant in food industry, antifungal activity against *Candida albicans, Saccharomyces cerevisiae, Lachancea thermotolerans, Metschnikowia pulcherrima*. antibacterial activity against *Escherichia coli, Salmonella typhi, Proteus Vulgaris, Klebsiella Pneumonae*, *Enterococcus Feacalis* and *Staphylococcus Aureus*.	Sharifi and Sharifi (2023)
Eucalyptus (*Eucalyptus globulus* Labill.)	Leaf	South eastern Australia	1,8- Cineole (oxygenated monoterpene), α-Pinene (monoterpene hydrocarbon), Aromedendrene (sesquiterpene hydrocarbon), Globulol (oxygenated sesquiterpene).	Antibacterial activity against *Staphylococcus aureus, Bacillus subtilis, Listeria innocua, Escherichia coli, Pseudomonas aeruginosa*, anti-qourum sensing activity, potential improving agent of conventional antibiotics against *Acinetobacter baumannii*.	Hafsa et al. (2016)
Ginger (*Zingiber officinale* Roscoe)	Root	Southern China and India	α- Zingiberene (sesquiterpene hydrocarbon), ar-Curcumene (sesquiterpene hydrocarbon), β-Sesquiphellandrene (monoterpene hydrocarbon), β- Bisabolene (sesquiterpene hydrocarbon), Camphene (monoterpene hydrocarbon).	Antibacterial activity against *Staphylococcus aureus, Escherichia coli, Xanthomonas oryzae* pv. *Oryzae, Ralstonia solanacearum*, *Bacillus* sp., *Klebsiella* sp., antifungal activity against plant fungi like *Rigidoporus microporus, Fusarium oxysporum, Pyricularia oryzae, Colletotrichum falcatum, Ganoderma boninense*.	Abdullahi et al. (2020)
Holy basil (*Ocimum tenuiflorum* L.)	Leaf	Indian subcontinent	Eugenol (monoterpene hydrocarbon), Camphor (oxygenated monoterpene), Estragole (phenylpropanoid), β-Caryophyllene (sesquiterpene hydrocarbon).	Antibacterial activity against *Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa* mortality agent of *Callosobruchus maculatus*, promising insecticide, antioxidant.	Bhavya et al. (2021)
Lemon (*Citrus limon* (L.) Osbeck)	Peel	Northeastern India	Limonene (monoterpene hydrocarbon), α- Pinene (monoterpene hydrocarbon), γ- Terpinene (monoterpene hydrocarbon), β-Pinene (monoterpene hydrocarbon).	Antifungal activity against *Eutypasp., Botryosphaeriadothidea, Fomitiporia mediterranea*, antioxidant.	Fancello et al. (2020)
Sage (*Salvia officinalis* L.)	Leaf, flower, stem, bud	Middle East and Mediterranean areas	1,8- Cineole (oxygenated monoterpene), Camphor (oxygenated monoterpene), Thujone (oxygenated monoterpene).	Antibacterial activity against *Pseudomonas aeruginosa, Staphylococcus aureus*, antioxidant, anti-Alzeimer, moderate anti-gout activities.	Farahpour et al. (2020)
Kakol (*Suaeda aegyptiaca* (Hasselq.) Zohary)	Leaves, Buds and Flowers	Iran	Geranyl-acetone, *p*-Vinylguaiacol, β – ionone	Improved storage quality and antibacterial activity against *Enterococcus faecalis*	Zibaee and Shamekhi (2023)
Cumin (*Cuminum cyminum* L.)	Leaf and seeds	Egypt, Turkey, India	Cuminaldehyde, *o*-cymene, *β*-Pinene	Radical scavenging agent and antibacterial against *Staphylococcus aureus*	Moradi et al. (2023)

(*continued on next page*)

Table 1 (*continued*)

Essential Oil	Source of EO	Primary incidence	Functional Compounds	Advantageous consequences	References
Clove (*Syzygium aromaticum* (L.) Merr. & L.M. Perry)	Leaves and Buds	Madagascar, Eastern Indonesia, Tamil Nadu	*m*-Eugenol, Carvone	Antifungal action against *Botrytis cinerea* in Plums	Oliveira Filho et al. (2023)
Bay leaf (*Laurus nobilis* L.)	Leaves	Himalayas, East India	*m*-Eugenol,Linalool, d-limonene, *α*-Pinene	Antifungal activity against Aflatoxic *Aspergillus flavus*	Singh et al. (2023)
Catmint (*Nepeta pogonosperma* Jamzad & Assadi)	Leaf, Buds, and Flowers	Europe, North America, South Aisa	Nepetalactone, 1,8-cineole, *α* – bisabolene	Antibacterial activity against *Klebsiella pneumoniae, Bacillus cereus,* and *Enterococcus faecalis*	Sharifi and Sharifi (2023)

4.1. Nanoemulsions as antimicrobial agents

Over the last few years, there has been a lot of inquisitiveness about the deployment of oil-in-water nanoemulsions for encasing biological antimicrobials, notably EOs (Fathi et al., 2021) which are water-resistant fluids extracted from various plants that frequently possess an array of antibacterial components. This is extremely likely since plants generate these compounds to safeguard against various kinds of enemies, such as microorganisms, insects, and herbivores. The major molecular processes underlying EO's antibacterial effect are believed to include the breakdown of microbial cell walls and obstruction of critical metabolic processes (Rao et al., 2019) (Fig 3). Because of the growing customer interest in clean-label foodstuffs, the food sector has been attempting to develop viable substitutes for the chemical antimicrobial compounds. (Patrignani et al., 2020) discovered that hexanal-nanoemulsions have been successful at deactivating both rotting and infectious bacteria in apple juice without affecting their attractive sensory qualities. Cinnamon oil nanoemulsions, have been demonstrated to be successful in controlling rotting and infectious agents (*Listeria monocytogenes* and *Salmonella* spp.) on melons (Paudel et al., 2019). Carvacrol nanoemulsions have been validated in studies to prevent microbial development (*Salmonella enteritidis* and *Escherichia coli* O157:H7) in infected mung bean, alfalfa, broccoli, and radish seeds (Pavoni et al., 2020). Antimicrobial nanoemulsions are additionally deployed in alimentary coatings and packaging components to extend the longevity of food (Panahirad et al., 2020). Thymol oil nanoemulsions incorporated films of gelatin have displayed good antibacterial efficacy, suppressing Gram-positive as well as Gram-negative bacteria (Li et al., 2020a). The nanoemulsions comprising cinnamaldehyde and garlic oil when incorporated in composite biopolymer films generated from gelatin and chitosan have exhibited good antibacterial capabilities against *Pseudomonas aeruginosa* (Pérez-Córdoba et al., 2018). Cherry tomatoes can be protected from rotting by molds like *Botritis cinerea* by coating with thymol nanoemulsions. After a week of storage at 5 °C, quinoa protein and chitosan edible covering comprising thymol nanoemulsion substantially suppressed the development of fungus on cherry tomatoes (Robledo et al., 2018).

4.2. Nanoemulsions as antibrowning agents

The hue and look of freshly cut vegetables and fruits are important quality indicators. The principal source of the unsuitable variations in the look of cut fruits and vegetables is the oxidation phenomenon mediated by the polyphenol oxidase enzyme. This enzyme transforms phenolic chemicals into darker-colored tints when it encounters oxygen. To circumvent this, the utilization of nanoemulsion to immobilize nanodroplets on the exterior of fresh foodstuffs has come to light as a potential option. The application of nanoemulsion coatings has been demonstrated as an efficient method for capturing the natural antioxidants or antibrowning substances in the oil phase, like carotenoids and alpha-tocopherol. When contrasted with the use of antioxidants by themselves, this technique has been recognized to minimize the browning score of fresh-cut fruits and vegetables. The traditional method for preventing undesired color shifts in sliced vegetables and fruits is to submerge them in a water-based solution containing antioxidants or antibrowning chemicals. A commonly employed antioxidant to regulate the enzymatic browning of sliced fruits and vegetables is ascorbic acid (Hasan et al., 2020). Antioxidants are likely to contribute durability over oxidation to formulations via one of the following options: serving as collaborators like tartaric acid, ascorbic acid, citric acid, citranoic acid, and phosphoric acid; hindering factors namely tocopherols, butyl hydroxytoluene, and ascorbic acid esters; or lowering elements such as sodium formaldehyde, ascorbic acid, metabisulfite, sodium bisulfite, and thiourea (Singh et al., 2017). New evidence confirms that these compounds are highly potent fat-soluble antioxidants, with just one monomer scavenging two radicals at once prior to deactivation. The use of such antioxidants can enhance the delay stage in the process of oxidation and their usage in nanoemulsions has received little attention and is nonetheless in its early stages (Dasgupta and Ranjan, 2018). Edible nanocoatings comprised of nanoemulsions infused with coloring and culinary substances, enzymes, antioxidants, antibrowning, and antimicrobial substances can be deployed to encase foods such as meat, dairy goods, fresh-cut vegetables and fruits, and sugary treats to improve preservation. Nanoemulsion-based treatments can restrict the exchange of gases as well as minimize losses of moisture and food deterioration (Donsì, 2018). Ascorbic acid, fibers, and minerals are abundant in pineapple, which is also prized for its distinct flavor and scent. Freshly cut pineapple has a very limited shelf life as the biological processes of the fruit are increased by chopping and chipping, which leads to fruit imperfections like textural breakdown, browning from enzymatic activity, contamination by microbes, and the formation of unfavorable chemicals. (Prakash et al. (2020) investigated the effects of sodium alginate-based nanoemulsions comprising varying amounts of citral (1.0, 0.5, and 0.1%) on the physicochemical, perceptual, and microbiological behaviors of the fruit. Fresh-cut pineapple samples coated with 0.5% and 1.0% citral showed higher color persistence, minimal oxygen consumption, and reduced bacterial invasion over the course of a 12-day storage

duration, indicating that these coatings could be deployed economically to extend the shelf life of fresh-cut pineapple.Plant constituents may be employed as long-lasting anti-browning treatments. Since there are scanty studies in this area, there are nevertheless encouraging possibilities that could be explored in subsequent research. It is widely acknowledged that when employed in conjunction with ascorbic acid, chemicals or infusions originating from plants may have superior anti-browning benefits.

Tyrosinase, for instance, is an enzyme that catalyzes unfavorable chemical processes in the food sector. It causes browning in drinks, fruits, and vegetables, which adversely affects the sensory and color features of these food items. This potentially reduces their longevity and selling prices while also diminishing their nutrient content during the harvesting processes. Certain Moraceous plants, such as *Artocarpus communis* J.R. Forst. & G. Forst., *Artocarpus integer* (Thunb.) Merr., and *Artocarpus heterophyllus* Lam., naturally contain artocarpanone (Arto), which has a potent tyrosinase-inhibiting effect. Nonetheless, Arto's poor water solubility restricts its potential application in the pharmaceutical, cosmetic, and food sectors. (Dong et al., 2016) created a microemulsion method to employ Arto (0.01%) and ascorbic acid (0.05% or 0.02%) as anti-browning ingredients in apple juice preservation. (Tao et al., 2017) verified the stabilizing flavonoid in a microemulsion encasing framework, but they did not reveal whether the encapsulation process had a beneficial impact on the anti-browning ingredients as there was not enough information to evaluate the deterioration of the liberated components over their shelf life.

A thorough investigation on the use of nano-encapsulated ascorbic acid for enhancing the preservation performance of freshly processed mushrooms was conducted by Ojeda et al. (2019). Different qualitative parameters (firmness, color and aesthetic appeal, phenolic constituents, and antioxidant ability) of the product were evaluated using a variety of procedures, which included a control, an ascorbic acid solution, a chitosan solution, chitosan dissolved in an ascorbic acid, and a chitosan/tripolyphosphate nanoaggregate solution containing ascorbic acid. According to their findings, the encapsulation approach effectively preserved the anti-browning and antioxidative properties of ascorbic acid as well as its dispersion from nanoaggregate frameworks in proximity to the product. Consequently, the standard of the preserved product was demonstrated to be higher, and the aging process initiation to be less pronounced. Intriguingly, they proved that the ascorbic acid and chitosan solution (non-nanostructured) and the chitosan treatment both had greater browning indices than the placebo solution.

4.3. Nanoemulsion as texture enhancing agents

It is commonly recognized that food processing activities (such as cleaning, pruning, or skinning) can affect the overall look of fruits and vegetables while diminishing their dietary content. The majority of these activities cause degradation to the exterior portion of vegetable and fruit tissues and, in numerous instances, stimulate biochemical responses that are primarily harmful to foodstuffs. Several researchers have reported such alterations as browning on the top, unusual flavor, diminished water retention, and textural degradation. Furthermore, organoleptic deterioration effects caused by the growth of microbes on the skin of vegetables and fruits have been documented, which need to be eradicated or minimized given that they promote consumer dissatisfaction besides posing a health concern; these constraints on processed fruits and vegetables ought to be reduced (Chaudhary et al., 2020). When juxtaposed with alternative procedures, nanoemulsions are more successful in their roles. Emulsifiers, maturation retarders, weighing intermediaries, and textural moderators are examples of stabilizers that may improve the kinetic longevity of nanoemulsions (Tripathi et al., 2021). Thickening or gelling compounds can be employed as supplements in nanoemulsions to change the topographical qualities, changing the mouthfeel, or improving the stability of the material. Texture enhancers can change the behavior of nanoemulsions within the human stomach along with the rheological properties and flavor of food products. Nanoemulsions have been additionally employed to enhance the smoothness and appearance of ice cream (Zeng et al., 2019). The downturn in consumer preference for fresh-cut fruits and vegetables is linked to cell wall stability and textural deterioration during preservation because of enzymatic breakdown. Edible coatings composed of nanoemulsions performed more effectively in improving the consistency of fresh-cut vegetables and fruits as exemplified by xanthan gum, a carbohydrate-based texture softener. The results demonstrated that xanthan gum-based nanoemulsions are effective in preventing the texture of fruits from diminishing (Hasan et al., 2020; Sathiyaseelan et al., 2021) studied the influence of calcium chloride ($CaCl_2$) and low molecular weight chitosan (LMWCS) and tea tree oil (TTO) nanoemulsion coatings on the flavor and texture of fresh-cut red bell pepper kept for 21 days at 4 °C. When contrasted to the control, the $CaCl_2$-LMWCS/TTO emulsion treatment sustained the total performance, perceptual activity, and textures of fresh-cut red bell pepper for 18 days. (Zhang et al., 2021) investigated the consequences of foliar application of an antibacterial nanoemulsion (carvacrol) on spinach. The findings showed that up on applying carvacrol nanoemulsions to the spinach leaves at minimal levels (0.005–0.5%), the plants stayed in good condition.

5. Applications of nanoemulsions in food industries

Nanoemulsions are widely recognized as exceptionally popular tactic deployed in food enterprises. Food-grade nanoemulsion technologies have been discovered to enhance the appearance, durability, sensory, and nutritional attributes of a variety of food-related goods. The deployment of nanoemulsions in food preparation improves the thermodynamic rigidity, visual candor, and homogeneous dispersibility. The prospective utilization of nanoemulsions in the flavoring, coloring, nutraceutical, and food packaging industries has tremendous potential for markets ((Dasgupta et al., 2019). Prospective applications of essential oil based nanoemulsion in the industries has been shown in Fig. 4.

5.1. Encapsulation of flavor and coloring agents

Food flavors comprise several compounds namely, allypyrazine, methoxypyrazines, 2-isobutyl-3-methoxypyrazine, acetyl-L-pyrazine, aldehydes, phenolics, and terpenoids. The preparative and atmospheric conditions impact numerous culinary flavor compo-

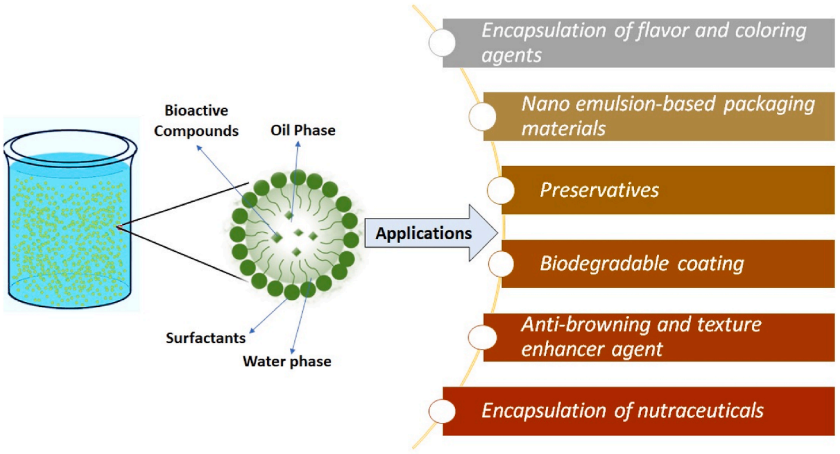

Fig. 4. Prospective applications of essential oil-based nanoemulsion which are the present scope of investigations.

sitions. As a result, encapsulating these chemicals in nanoemulsions is a sensible approach to retaining their operational and architectural characteristics. The creation of nanoemulsions including culinary flavors such as mint or peppermint citral, beta-carotene, and D-limonene have been recently documented using various elemental constituents namely medium-chain triacylglycerol (MCT) starch, MCT buffer solution, and maltodextrin (Shishir et al., 2018). The common functional groups of the flavors and coloring chemicals deployed in food are aldehydes, ketones, and esters, which render them sensitive to oxidative and photolytic destruction. These compounds can be encapsulated through nanoemulsions to avert these adverse consequences and extend their storage period. Citral nanoemulsions were initially created to improve their durability. The molecular durability of an O/W nanoemulsion of citral coupled with naturally occurring antioxidants like b-carotene, tanshinone, and black tea extracts was excellent throughout preservation. The nanoemulsions were made with lecithin-stabilized kernels of palm lipid in a pH 3 buffer with a 1:1 citral/antioxidant proportion. Antioxidant encasing reduced the development of undesirable flavoring molecules such as *p*-dimethylstyrene and *p*-methylacetophenone. including the products from the breakdown of lipids. Gelatin and Tween 20 were employed as emulsifiers in the food sector to protect citral against deterioration amid corrosive circumstances (Tian et al., 2017).

Pigments offer plants their naturally brilliant color, the most ones present in fruits and vegetables being red-yellow betalains, green chlorophylls, red-purple anthocyanins, and yellow-orange carotenoids. Besides their coloring capabilities, many plant pigments may have health-promoting benefits. Numerous lipophilic colorants, like paprika, lycopene, beta-carotene, and additional carotenoids, are naturally accessible and utilized in foodstuffs. They can be used as pigments or colorants in food due to their organic nature (Kiokias et al., 2016). Natural colorants are safe food enhancers that can be used to offer natural color and have the ability to boost immunity and avert maladies as therapeutic agents. Encapsulation is the ideal pathway to stabilize and improve the utilization of plant pigments (Ghosh et al., 2021). By encapsulating the emulsion with starch caseinate and chitosan epigallocatechin-3-gallate conjugates, the physical and chemical characteristics of b-carotene nanoemulsions have been enhanced (Wei and Gao, 2016). Cantaloupe melon has been exploited as a source for carotenoids. These carotenoids' nanoemulsions have better dissolution in water and color permanence; carotenoids' dissolution in water was improved using gelatin.

According to (Medeiros et al., 2019), the yogurt that utilized nanoemulsions as organic coloring agents remained consistent for 60 days. A different investigation entails enhancing the long-term viability of acid-simulated drinks with astaxanthin by supplementing nanostructured lipid carriers applying antioxidants like tocopherol and EDTA; nanoemulsion has a particle size of 94 nm and is more stable (Tamjidi et al., 2018).

5.2. Encapsulation of nutraceuticals

Nanoencapsulation procedures create vital nanosuspensions that are coated or encapsulated with a combination of dried or liquid wall materials. The chemical composition of nutraceuticals can be preserved through the effects of environmental elements such as sunlight, oxygen, acidity, reactive oxygen species, and temperatures. It allows for tailored administration, increased accessibility, and regulated diffusion of encapsulated drugs (Tahir et al., 2021). Furthermore, the encapsulation of nutraceutical molecules enhances their dissolution. Consequently, the features acquired by nutraceuticals are dependent on the physical and chemical characteristics of the vesicles with regard to an encased compound (Paolino et al., 2021). Encapsulation of bioactive substances including nutraceuticals, has garnered a lot of attention in the past ten years. Comprehensive evaluations with accumulated data on the utilization of various encapsulation procedures and encapsulating media have been performed for a wide range of bioactive compounds (Jacobsen et al., 2018). Several cancer-fighting plant-derived nutraceuticals, like resveratrol, quercetin, curcumin, genistein, and epigallocatechin gallate, are currently incorporated within nanoliposomes (Dutta et al., 2018) and polymer-based sustainable nanoparticles (Illahi et al., 2019). When compared to nutraceuticals by themselves, anticancer nutraceuticals incorporated into nanoparticles exhibit better dissolution, incorporation, accessibility, and antitumor potency. However, until recently, only a few investigations adequately examined these nanostructures in authentic food systems. Encapsulated polyphenols and vitamins can be incorporated into a variety of culinary goods while maintaining stability. Even so, various factors, namely the optimum encapsulating framework, the perfect core-

to-carrier proportion, and the best possible functional settings, ought to be assessed (Lopes and Brandelli, 2018). The present research suggests that tocosomes and nanoliposomes could be used as potential vehicles to encapsulate and deliver nutraceuticals in food systems. Nanocarriers can boost the evident dissolution of hydrophobic nutraceuticals without affecting the sensory nature of foodstuffs (Assadpour and Mahdi Jafari, 2019). The combinatorial distribution of tocopherol and ascorbic acid, or tocopherol and glutathione, to increase antioxidant activity in food items, and the stabilization of certain minerals (such as calcium and iron) in dairy and other drinks has been documented (Zarrabi et al., 2020). Xanthophyll encapsulation and shielding in nanoemulsions have received far less attention than carotenes. The bioaccessibility of astaxanthin contained in nanoemulsions was assessed by (Liu et al., 2018) using a virtual gastrointestinal tract. Microfluidization was used to create these nanoemulsions from various long-chain triglycerides (flaxseed, olive, and corn oils). (Chuacharoen and Sabliov, 2019) examined the potential of nanoemulsions and biopolymer nanoparticles to stave off the chemical breakdown of curcumin throughout its manufacturing and preservation in an exemplar culinary system. They used identical emulsifiers (lecithin and Tween 80) to make nanoemulsions (medium-chain triglycerides) and biopolymer nanoparticles (zein). The biopolymer nanoparticles were more successful than the nanoemulsions at preserving curcumin from deterioration under atmospheric conditions (such as pH and temperature). Persistent storage investigations, nonetheless, revealed that the curcumin entrapped in the nanoemulsion was more successfully preserved when compared to the nanoparticles. Likewise, (Hong et al., 2019) employed nanoemulsions to contain extracts of turmeric instead of curcumin. In another study, extracts from tomatoes with an abundance of lycopene and curcumin, two antioxidant intermediaries, were encapsulated within the structure, demonstrating the nanoemulsions' potential as nutraceutical medication delivery methods. The goal of this research was to shield cardiac myoblast tissues from the damaging impacts of the potent anticancer drug doxorubicin. In comparison to nanoemulsions comprising simply doxorubicin, the suggested nanoemulsions, particularly ones containing lycopene, increased the survival of cells by 35–40% and decreased the secretion of interleukins (IL) IL-1, IL-6, IL-8, nitric oxide, and tumor necrosis factor TNF-alpha (Quagliariello et al., 2020).

5.3. Nanoemulsion-based packaging materials

Antimicrobial nanoemulsions were additionally used in culinary coverings and materials for packaging to extend the longevity of food. Before creating coated surfaces or films, the nanoemulsions are frequently combined with polymers from natural sources. In the course of time, the EOs progressively seep off from the coatings or films, helping to eliminate or restrict the expansion of bacteria, yeasts, or molds. With respect to the size of the pores and connections throughout the polymer infrastructure, EOs could spread across the films as distinct entities or as droplets of oil (Hasan et al., 2020). Thymol-, cinnamaldehyde-, and eugenol-based nanoemulsions, for instance, have been integrated into biodegradable films produced from pullulan, and their dissolution characteristics have been investigated (Tonyali et al., 2020). Thymol oil nanoemulsions placed into films of gelatin have exhibited excellent antibacterial action (Li et al., 2020b). Thymol was gradually expelled from the gelatin films and inhibited both, the Gram-positive and Gram-negative bacteria. Essential nanoemulsions comprising cinnamaldehyde and garlic oil were placed onto blended biopolymer films produced with gelatin and chitosan which revealed good antibacterial capabilities against *Pseudomonas aeruginosa* (Pérez-Córdoba et al., 2018). Consequently, *Thymus daenensis* Celak. oil-based nanoemulsions were additionally found to possess remarkable antibacterial characteristics when mixed with hydroxypropylmethylcellulose edible films (Moghimi et al., 2017; Pinheiro Bruni et al., 2020) examined the cinnamon essential oil encased in cyclodextrin nanosponges for usage in antimicrobial packaging; bacteriostatic action towards the germs was examined. The prospective application of pectin films incorporating marjoram EO-loaded nanoemulsions and pickering emulsions in alimentary packaging has been evaluated (Almasi et al., 2020); active pectin films incorporating pickering emulsions have a high potential for antimicrobial packaging. To inhibit the spread of *Botrytis cinerea* in grapes, the oil-entrapped emulsion was used to encase clove and lavender EOs, as well as vanillin, within chitosan and alginate beads (Sangsuwan and Sutthasupa, 2019; Cheng et al., 2019) generated encapsulated carvacrol in cyclodextrin/sodium alginate films and tested their antifungal activities in white mushrooms preserved at 4 °C. The ideal EO content in the encapsulating structure was 15 g/L for *Trichoderma* sp., and the films increased the amount of active free-radical neutralizing enzymatic agents, which alleviated oxidative harm and retarded the withering of postharvest mushroom. Table 2 summarizes various patents registered in the area of EO- based nanoemulsion.

6. Disadvantages and sustainability aspects of nanoemulsions

The drawbacks associated with the deployment of nanoemulsions include the expensive nature of manufacturing processes and the difficulty in locating an edible surfactant, as well as the reality that they are almost thermodynamically unsettling owing to a variety of variables. They comprise environmental and inherent variables, which entails amalgamation, creaming, maturation, flocculation, etc., instantaneous biologically active ingredient expulsion, and preservation uncertainty (Peng et al., 2019). Some of the problems, for example, are the dearth of consistency in EO behavior. Notwithstanding their wide range of chemical nature, EOs can exhibit both qualitative and quantitative alterations in their levels of bioactive substances, leading to a variety of outcomes (Fig. 5). The nanoemulsion systems utilized for encasing of compound should also be designed with the goal of disguising the savory flavor of the EO ingredient throughout antimicrobial conservation. It is likely that EOs are unsuccessful in coatings in relation to in vitro assessment, which might be linked to the food's intricacy. The chemical intolerance that may develop among the EOs and the matrix of the films, wrapping, or foodstuffs, may have a detrimental impact on the antimicrobial efficacy for nanoemulsion-based coating or film production (Moreira Gonçalves et al., 2020). There appears to be fewer directed deliveries of nanoemulsion-based food storage technologies. NEs require a substantial amount of surfactants and cosurfactants to stabilize the nanodroplets, and their capacity to dissolve high-melting compounds is hindered (Jeya Jeevahan et al., 2020). Nanoencapsulation comprise a significant approach for encapsulating EOs and bioactive ingredients with the goal of improving microbiological antagonistic functions, antioxidant capabilities, and utilization in practical food production processes (Chaudhari et al., 2021). The diminution of unbound EO bioavailability at

Table 2
– Patents registered on nanoemulsions over the last decade.

Patent No	Patent Title	Year	Country	Major outcomes of the invention	References
US 201902 01338A1	Compositions for NE Delivery Systems	2019	United States	The NE system promises for extremely favorable particle size distribution, optical clarity, and product stability against Ostwald ripening with high levels of oil concentrations. Active agents with poor water solubility can be incorporated in the NE systems to improve their solubility/stability in aqueous medium or to enhance their delivery for use in various applications including food.	Huang (2015)
US 20190388308A1	Novel NE comprising glycerol in aqueous phase	2019	United States	NE is processed in a one-step process yielding droplets of size 20–400 nm by homogenizer.	Quan (2018)
WO 2018122598A2	Curcumin-loaded NEs, method of manufacture, and method of preventive treatment using the same	2018	Chile	The O/W curcumin-loaded NE is preventive for metastatic cancer by applying topically to an area of an excised primary tumor, and monitoring any re-incidence of metastatic cancer in the excised primary tumor area.	RIVERA SJ et al. (2018)
US 9884299B2	Process for the preparation of W/O and O/W NE	2018	Italy	Process for the preparation of a W/O or O/W NE with droplet diameter ranging from 1 to 500 nm and characterized by an interface tension lower than 1 mN/m	Del Gaudio L et al. (2018)
US 10016364B2	Compositions and Methods for Making and Using NEs	2018	United States	Improved NE systems comprising uniform nano-sized particles (< 97 % of them with 10–110 nm in diameter, and the difference between min and max diameters not exceeding 600 nm) resulting in improved bioavailability of incorporated compounds such as nutraceuticals	Nicolosi R and Wilson T (2018)
US 9649275B2	NEs	2017	Australia	The O/W NE processes for their preparation and use as delivery vehicles of active components for various applications including food and agriculture.	James Wooster et al. (2017)
US 20150051298A1	Methods for producing optimal stable NEs and formulations obtained therefrom	2015	United States	The method for producing stable NE having a desired droplet size and functional properties tailored for use in a specific application, which is referred to as substantially optimizing composition of aqueous and organic phases	McClements DJ et al. (2015)
US8628690B2	NE compositions and methods of use thereof	2014	United States	NE composition may include ingredients or a synergistic blend of non-reducing sugars, sugar polyols, MCT, polysaccharides, polyphenols, phospholipids, chitosan, proteins, glycopeptides, phosphopeptides, and provides enhanced oxidative stability, emulsion stability, and health benefits such as prevention of hypercholesterolemia or bone (and teeth) mineral loss.	Mora-Gutierrez A and Gurin MH (2014)
US 201300 64954A1	ME Concentrates and NE Flavorant Compositions for Food Applications	2013	United States	The hydrophobic food flavorant has a droplet size in between 50 nm and 100 nm and the composition is free of polyols other than the sugar alcohol via described NE composition	Ochomogo M et al. (2013)
US 20120052126A1	NE Containing Antioxidants and Other Health-Promoting Compounds	2012	United States	The NE particles having diameters < 500 nm, encasing antioxidant and, optionally, other health-promoting compounds, wherein the NE are relatively stable for prolonged periods bevewithout significant change in physical properties and are suitable for administering to humans and other mammals orally, topically, intravenously, transdermally, and subcutaneously.	Pathak Y and Tran HT (2012)

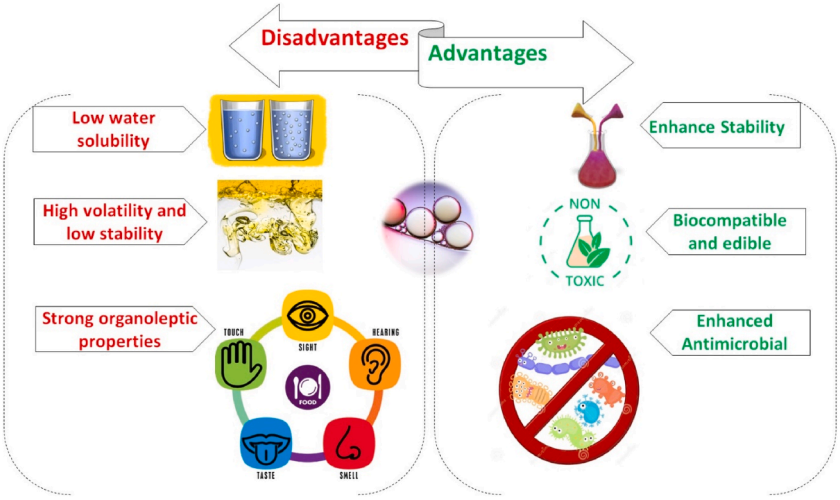

Fig. 5. Highlights and Challengers for the Potential Application of essential oil based nanoemulsion.

treated surfaces of food following a brief amount of time limits the possibilities in the food system. Monitoring the release may thus be of great relevance in improving the lifespan of stocked food items. The antioxidant properties of *Cinnamodendron dinisii* Schwacke EO were also retained after inclusion in a chitosan matrix, according to the authors. (Mahdi et al., 2021b) found that encapsulating *Citrus reticulata* Blanco EO in hybrid wall materials made of whey protein isolate, maltodextrin, and gum arabic improved its stability against oxidation. Furthermore, nanoencapsulated EOs have been shown to have greater antioxidant capacity and dissolution, as well as resistance to temperature change (Yang et al., 2021). Because the pungent flavor and odor associated with certain EOs may alter the sensorial characteristics of processed foodstuffs, nanoencapsulation might be used to promote regulated delivery and therefore sensory property retention. Industrial-scale, feasible suggestions of EOs and nanoemulsions as efficient food preservation agents necessitate quality assurance without any detrimental impacts on mammals to render them beneficial for consumers. This is in conjunction with microbiological contamination and toxins suppressive effectiveness. Several international organizations, including the Flavor and Extract Manufacturers Association, the Food and Drug Administration, the Codex Alimentarium, the Council of Europe, and the Food Chemical Codex, have verified specific methods for the toxicological and chemical analysis of EOs. During actual utilization, they also noted hostile and beneficial effects for some EOs in mammals (Falleh et al., 2020). In this regard, *Petroselinum crispum* (Mill.) Fuss essential oil (PEO) and PEO contained in chitosan were evaluated for damage in mice, and the Lethal Dose (LD) LD50 values were discovered to be 10,765 and 26,830 mg/kg body weight, respectively (Deepika et al., 2021). In an investigation conducted by (Das et al., 2021), the acute oral exposure of *Pimpinella anisum* L. essential oil (PAEO) and chitosan nanostructured PAEO was evaluated in mice; LD50 values were shown to be 19,879.89 and 13,641.35 l/kg body weight, respectively. They hypothesized that a tiny nanoemulsion is containing greater EO in each nanocapsule and a lower average lethal dosage may be the cause of the decreased LD50 reading for nanostructured PAEO. Another study by Dwivedy et al. (2018) determined the average lethal dosage of *Illicium verum* Hook. f. essential oil (IvEO) on male mice to be 11,257.14 l/kg body weight. Increased LD50 readings for EOs and nanoemulsions compared to conventional artificial preservatives for food such as bavistin (1500 mg/kg), nystatin (8000 mg/kg), and lindane (59–562 mg/kg) reinforce their use as eco-friendly and secure additives in the food and agricultural sectors. Fig. 5 describes various prone and cone for essential oil based nanoemulsion used in various food industries.

7. Future perspective and conclusion

Essential oils offer antimicrobial effect aimed at microorganisms found in foodstuffs. Nevertheless, their extreme hydrophobicity and powerful influence on the taste and texture of food items, the risk of allergic reactions, and to a large extent the development of microbial resistance, render their inclusion within culinary systems to be a significant challenge. Consequently, encapsulating these oils might provide potential remedies for the aforementioned problems. In broad terms, only a few investigations have dealt with the utilization of contained essential oils in actual dietary platforms, whilst even fewer cases have explored encapsulation using emulsions generated by the protective membranes. Prospective studies may concentrate on the efficacy of multiple essential oils and their blends contained in various viable food and beverage production processes. The integration of emerging emulsification strategies to oil-based packaging, like membrane emulsification, may offer novel alternatives for easy and trustworthy encapsulation approaches aimed at food-related applications.

In conclusion, considering the increasing fascination in the use of essential oils, public safety issues have been acknowledged as a priority. While various organizations have worked with governing bodies to adopt essential oil legislation globally, standardization in regard to formulation and dosage, consumption, and potentially harmful consequences, need to be maintained up to date.

CRediT authorship contribution statement

Conceptualization, L.N.S.V., B.M., Y.K.M. and A.K.M.; original draft preparation, B.M., L.N.S.V. and Y.K.M.; writing—review and editing, R.S.V.; visualization, B.M., B.N., and R.S.V.; supervision, R.S.V. All authors have read and agreed to the published version of the manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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Effect of semi batch and fed batch addition of glucose on alkaline protease production: a multi-objective optimisation approach

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Abstract: Alkaline protease is one of the important enzymes in many industries. In this effort, semi batch addition and fed batch addition of glucose have been considered for maximisation of protease concentration in minimum fermentation time. The kinetic model of the process is validated with the experimental batch and fed batch addition of glucose from the open literature. A theoretical study has been conducted with such a validated model to check the effect of protease concentration on the semi batch addition of glucose. Based on this, multi-objective optimisation studies have been done for the simultaneous minimisation of fermentation time and maximisation of protease concentration with the relevant constraints. The elitist non-dominated sorting genetic algorithm (NSGA II) has been utilised for this purpose. The additions of glucose in semi batch mode show the potential increasing of protease concentration in at a less fermentation time as compared to the batch experimental data.

Keywords: protease; semi-batch addition; fed-batch; NSGA II; multi-objective optimisation.

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1 Introduction

Because of their efficacy as catalysts, and their cost effectiveness and biodegradability, enzymes are revolutionising the biotech industry. The global market for industrial enzymes, from $5.5 billion in 2018, will hit $7.0 billion by 2023 (Arun, 2018). Among the hydrolytic enzymes, peptidases or proteases are one of the most significant classes of extra-cellular microbial enzymes and are commonly used in several industrial sectors, in particular in detergents, milk, medicines, oil, leather and silk, apart from waste treatment (Scheuer, 1990), accounting for more than 65% of the total industrial enzyme industry (Annamalai et al., 2014). The importance of this enzyme in industry scenario motivates further gaps in the production of enzymes to be studied. The enzyme can be produced from various sources, and the most cost-effective source is from bacteria.

Currently, a large proportion of the commercially available proteases are derived from *Bacillus* strains (Rawlings et al., 2010, Ahmed et al., 2013). This is mainly due to the high capacity for protein secretion that several *Bacillus* species possess and downstream processing of the enzyme production is simpler, resulting in more than 20 g/L proteins (Harwood and Cranenburgh, 2008, Gimenes et al., 2021). These are also reasons for the large number of patents and commercial proteases from *Bacillus strains* (Vetter et al., 1993, Merkel et al., 2009). Proteases are generally produced using submerged fermentation (SMF) due to its apparent advantages in consistent enzyme production characteristics with defined medium. Process conditions and advantages in downstream in spite of the cost-intensiveness for medium components whilst the production of these biocatalysts using agro-biotech substrates under solid-state fermentation (SSF) conditions provide several advantages in productivity (Contesini et al., 2018), cost-effectiveness in labour, time and medium components in addition to environmental advantages like less effluent production, waste minimisation, etc. (Pandey et al., 2000).

Because of high industrial demand of this enzyme, production of this enzyme is extensively studied; however, not much is discussed in the kinetic study of protease activity. Maximum productivity of proteases either in SMF or SSF from microorganisms in lesser time is essential for industrial scale operations. Influence of parameter like concentration of substrate greatly influences enzyme production and production time need be optimised for greater yield. Singh et al. (2004) reported that excess glucose feeding extended fermentation time and reduced the enzyme productivity. There is a need for optimisation of batch and semi batch addition of glucose concentration for maximising the yield and minimising Time. For modelling biological system kinetics should be very well defined. Many nonlinear differential equations and unstructured models are used for describing the biological system. In this regard, we need to identify the kinetics of the biochemical reactions and optimise the process parameters using multi-objective optimisation (MOOP), non-dominated sorting genetic algorithm (NSGAII) (Deb, 2001) for enhanced production.

In this study, three MOOP case studies were conducted with the validated kinetic model for the batch and fed batch glucose addition that are given by Ghovvati et al. (2015) has been considered and is validated against the experimental data (Ghovvati et al., 2015). Solving more than one objective simultaneously with relevant constraints is demanded by the real world. To cater this, three multi-objective optimisation studies have been considered. The additions of glucose in semi- batch mode (glucose addition at intermediate intervals) have been considered in the first two MOOP cases. As the fermentation time (t_f) increases, protease concentration also increases. Therefore, a need was observed to find the optimal processing conditions for the desired conflicting objectives (i.e., minimisation of fermentation time and maximisation of protease concentration). Similarly, MOOP study has been conducted for the fed batch addition of glucose for the desired confliction objectives (i.e., simultaneous minimisation of fermentation time, minimisation of glucose concentration and maximisation protease concentration).

2 Model and problem formulation

Anvari and Khayati (2011) conducted the experiments in the below conditions. The bacterial strain *Bacillus licheniformis* (MG5) was grown and maintained in nutrient broth in a 500 ml shake flask with 100 ml medium (Ghovvati et al., 2015). Separately sterilised glucose was added to the medium as a carbon source just before inoculation. The cultures were inoculated and incubated at 35°C and 150 RPM. The reactions were carried out for 32 hours with 40 g/l initial concentration of glucose in batch mode and fed batch mode with a flow rate of 0.01 l/h.

The below mentioned set of ordinary differential equations [i.e., equation (1)] explains the fermentation process (Ghovvati et al., 2015). X, S, P, t, μ and μ_{max} [i.e., equation (2)] denotes the cell mass concentration, substrate concentration, product concentration, fermentation time, specific growth rate and the maximum specific growth rate respectively. These equations describe the cell mass concentration dynamics, substrate concentration dynamics and the product formation rate respectively (Ghovvati et al., 2015). In these equations, $Y_{X/S}$, m_s, S_0 and k describes the biomass yield per unit mass of substrate, maintenance coefficient, initial substrate concentration and the saturation constant for the enzyme (Ghovvati et al., 2015). The microorganism's growth during the conversion is a complex process. The kinetic model describing the fermentation is crucial for understanding the cell growth and substance development in a quantitative way. The Contois growth model has been considered in the present study as it is describing the experimental data very well (Ghovvati et al., 2015). In these equations, inlet flow rate (i.e., f) is equal to zero for batch mode of addition. The parameters of this model for the batch and fed batch are shown in Table 1 (Ghovvati et al., 2015). The above system of ordinary

differential equations has been solved by differential algebraic (DAE) solver LIMEX (Deuflhard et al., 1987) with the kinetic parameters given by Ghovvati et al. (2015). To find a high protease concentration, one may end up with more fermentation time when the fermentation is conducted in batch mode. In other words, to find protease in less fermentation time, one may get less protease concentration. A semi batch, multi objective optimisation study (MOOP) study is, therefore, performed here to obtain trade-off solutions in the above mentioned conflicting scenario. Semi batch mode of addition of glucose has a great potential to increase the product concentration in less time. Study of maximisation of protease concentration and the effect of the semi batch addition of glucose on product concentration in less fermentation time is important. By keeping the above two objective functions (i.e., minimisation of fermentation time, maximisation of protease concentration), minimising the sum of the additions of glucose in semi batch study is included as the third objective function in the second multi-objective optimisation (MOOP 2) study to observe the effect of process parameters. In both cases, the decision variables are glucose addition amounts (u_1, u_2, u_3, u_4) at different time instances and total fermentation time (t_f). Once t_f is decided by optimiser, t_f is divided into four equally spaced instances of time including time $t = 0$, where glucose will be added. The amounts of glucose to be added at these time instances are decided by the optimisation routine. All fivev decision variables (t_f, u_1, u_2, u_3, u_4) lie between their lower and upper bounds. The sum of glucose additions is forced to lie near the experimental values to reduce the extrapolation errors.

The main aim is to achieve maximum product concentration in less fermentation time with less glucose addition. The above two multi-objective formulations has been thoughtfully designed and is given in Table 2. To solve the above two MOOP problems (MOOP 1 and MOOP 2), real coded non-dominated sorting genetic algorithm (NSGA II) (Mogilicharla et al., 2014) has been utilised. In another study (i.e., MOOP 3), MOOP study for the fed batch case is also considered based on the experimental data (Ghovvati et al., 2015). The initial glucose concentration for the batch and fed batch mode was 40 g/l and the flow rate was 0.01 l/h. In this case (i.e., MOOP 3), the glucose concentration (u), the flow rate (v) and fermentation time (t_f) limits for this optimisation study is given in Table 3. In this, the limits of the glucose flow rate have been kept within the ±20% of the experimental limits and the concentration of glucose less than or equal to experimental value from the open literature (Ghovvati et al., 2015).

$$\begin{aligned}
\frac{dx}{dt} &= \mu X - K_d X - \frac{fX}{V} \\
\frac{ds}{dt} &= -\frac{1}{Y_{X/S}}\mu X - m_s X\frac{S}{k+S} - \frac{f(S_o - S)}{V} \\
\frac{dP}{dt} &= \alpha\mu X - K_p P - \frac{fP}{V} \\
\frac{dV}{dt} &= f
\end{aligned} \tag{1}$$

where

$$\mu = \frac{\mu_{\max} S}{k_x X + S} \tag{2}$$

Table 1 Kinetic parameters for both batch and fed batch

S. no.	*Parameter*	*Batch*	*Fed batch*
1	$\mu_{\max}$	0.7000	0.6384
2	K_d	0.0146	0.0010
3	$Y_{x/s}$	0.5825	0.7387
4	m_s	0.0134	0.0139
5	α	0.774	0.5848

Source: Ghovvati et al. (2015)

Table 2 MOOP formulation for semi-batch addition of glucose

Case 1	*Case 2*
Minimise t_f	Minimise t_f
Maximise P	Maximise P
	Minimise $(u_1 + u_2 + u_3 + u_4)$
Subjected to	
$u_1^{\min} = 10, u_1^{\max} = 10$	
$u_2^{\min} = 0, u_2^{\max} = 20$	
$u_3^{\min} = 0, u_3^{\max} = 20$	
$u_4^{\min} = 0, u_4^{\max} = 20$	
$16 \le t_f \le 32$	
$\sum_{i=1}^{4} u_i \le 40$	

Table 3 MOOP 3 formulation for fed batch process

Minimise tf
Maximise P
Minimise S
Constraints for fed batch
$S \le 40$ g/l
$0.008 \le f \le 0.012$ *l/h*
$16 \le t_f \le 32$

To perform MOOP study, LIMEX (DAE solver) (Deuflhard et al., 1987), embedded with model, has been integrated with real coded NSGA II optimisation routine. In real coded NSGA II, each decision variable is a gene and a chromosome is composed of all the decision variables participating in the optimisation. There are N chromosomes in the optimisation, which are generated randomly within the range. In the present first two cases (i.e., MOOP 1 and MOOP 2), each of the N chromosomes is a cluster of five decision variables (t_f, u_1, u_2, u_3, u_4) and in a population of N, 5N such real numbers are randomly generated. Once this random creation is over, objective functions and constraints

are calculated from the model. Children population of size N are created by using genetic operators (i.e., crossover and mutation) from the parent population. As NSGA II is an elitist approach, children and parent population are merged together to yield a population size of 2N. From that, based on the non-dominated sorting and selection, only N solutions are carried over to the next generation (Deb, 2001). This procedure continues with the predefined number of generations. In the present study, the following NSGA II parameters are used to perform MOOP study: maximum number of generations = 100, N = 100, distribution index for real coded crossover = 0.01, distribution index for real coded mutation = 0.01, crossover probability = 0.9, mutation probability = 0.1.

3 Results and discussion

In the present study, the kinetic model and kinetic parameters that are given by Ghovvati et al. (2015) has been considered and is validated against the experimental data (Ghovvati et al., 2015) for the batch and fed batch addition of glucose. Ghovvati et al. (2015) presented various growth kinetic models and estimated the kinetic parameters by hybrid genetic algorithm/particle swarm optimisation for batch and fed batch mode. They reported (Ghovvati et al., 2015) that to explain the alkaline protease production, Contois model exhibits better fit with the experimental data (Ghovvati et al., 2015) as compared to the other models. In this work, Contois model has been validated by comparing the biomass concentration, glucose concentration and protease concentration with the experimental data (Ghovvati et al., 2015) for batch case and fed batch case and is shown in Figures 1 and 2. These are well correlated with the experimental data. It is evident from the Figure 1 and Figure 2 that glucose concentration plays a vital role in the biomass production and protease concentration in both cases.

The main aim here is to get the maximum protease concentration in less fermentation time. When fermenting in batch mode, it is possible to end up with extra fermentation time in order to achieve a high protease concentration. To put it another way, finding protease in a shorter fermentation period may result in a lower protease concentration. In the above-mentioned conflicting scenario, a semi-batch, multi-objective optimisation research (MOOP) is conducted to obtain trade-off solutions (represented in Table 2). One of the ways to achieve maximum protease concentration is to change the mode of operation of glucose addition from batch to semi batch addition (i.e. addition of glucose at different intervals). So, finally we need to maximise protease concentration in minimum fermentation time with relevant constraints and limits (MOOP 1: Table 2). The elitist non-dominated sorting genetic algorithm (NSGA II) has been utilised to find the Pareto optimal (PO) solutions. Multi-objective Pareto solutions for the first optimisation case (MOOP 1) are obtained among two conflicting objectives and are represented in Figure 3. There are multiple numbers of optimal solutions in Figure 3 which are all equally important are also known as non-dominated solutions. Trade-off among these solutions is evident as the enhancement in certain objective comes at the cost of deterioration of another objective. For example, to get protease of high concentration, one has to compromise in fermentation time. Nonetheless, at the conclusion of the optimisation analysis, only one solution has to be selected as the method of preference and this choosing requires the expertise of the decision-maker on how to balance the different objectives. The experimental points with high protease concentration have been shown in the same figure with filled points. It is observed that the semi batch addition of glucose exhibits superior in performance as compared to the batch experimental data. The discrete amount of additions of glucose is shown in Figure 4 that corresponding to the Pareto solutions (Figure 3). In this, most of the points are shown at glucose concentrations in the ranges of around 32, 6.5, 0.65 and 0.02 g/l (initial addition, 1st addition, 2nd addition and last addition). These points are added with straight lines to see if there lay trends among the addition points. Glucose additions are monotonically decreasing. Here one should note that the selection of the values of these decision variables could have been anywhere in the given bounds.

Based on the above optimisation study, another optimisation study has been carried out, in which one more objective function has been included apart from the above mentioned conflicting objectives to observe any improvement. In this second optimisation study (MOOP 2), minimisation of fermentation time, maximisation of product concentration (i.e., protease concentration) and minimisation of the sum of the glucose addition amounts have been considered as these three objective functions are conflicting in nature. The corresponding Pareto optimal solutions for this problem are represented in Figure 5. For the clear pictorial representation, three dimensional points are projected on to the two-dimensional planes. In the same Figure, experimental points with high protease concentration are represented with filled points (encircled). For a particular optimal point, various combinations of glucose additions are possible. These optimal glucose additions will be decided by the optimiser in the given bounds provided. The optimiser has chosen a wide variety of optimal solutions to minimise the sum of the additions of glucose apart from the other two objective functions as compared to the MOOP 1. The discrete additions of glucose for the above corresponding Pareto is represented in Figure 6, which are joined by straight lines. Glucose additions are showing the similar behaviour which is monotonically decreasing (shown in Figure 6) with time like earlier case. A wide variety of glucose combinations are possible as compared to the earlier case, which is due to the inclusion of minimisation of the total glucose addition as one of the objective function. With this, almost same protease concentration has been obtained with less amount of glucose as compared to the experimental data (Ghovvati et al., 2015), which was conducted in batch mode. One of the observations made in this study is with the similar

process conditions can fetch higher protease concentration (MOOP 1) and with the less glucose addition almost same protease concentration (MOOP 2) have been obtained, which is represented in Table 4 (e.g., almost 7% less in fermentation time with almost same protease concentration and around 6% improvement in protease concentration in almost same fermentation time).

After observing the trends in the above two MOOP cases (i.e., semi-batch glucose addition), another optimisation study (MOOP 3) has been carried out for the fed batch addition of glucose. The problem formulation is provided in the Table 3. The objective functions in this study are the simultaneous minimisation of fermentation time, minimisation of initial glucose concentration and the maximisation of protease concentration with the relevant constraints, which are bounded based on the experimental data (shown in Table 3). The resultant Pareto optimal solutions are shown in Figure 7. It is evident from the Figure 7 that a well spread of points have been obtained on the entire range of objective functions. A fed batch experimental point of having high protease concentration has been shown for the comparison with the MOOP 3 and is shown in Table 5. It was observed that with the less glucose (as compared to the experimental) slightly more protease concentration has been obtained. And in some cases, protease productivity has been increased with less glucose concentration. Most of the optimal points are moved towards the lower range of glucose flow rate (i.e., around 0.008 l/h). This also exhibited improvement in process performance as compared to the fed batch experimental data from the open literature.

Figure 1 Comparison of concentrations between the experimental values and the model prediction for the batch glucose addition (see online version for colours)

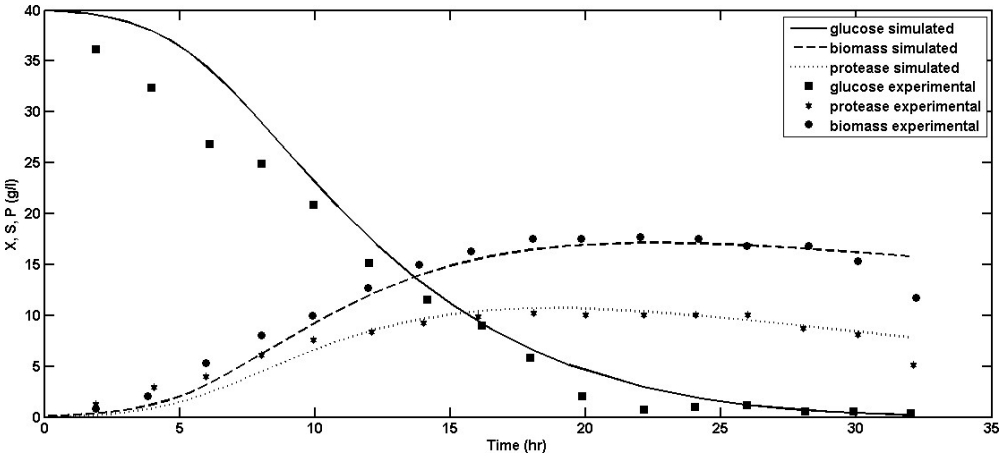

Figure 2 Comparison of concentrations between the experimental values and the model prediction for the fed-batch glucose addition

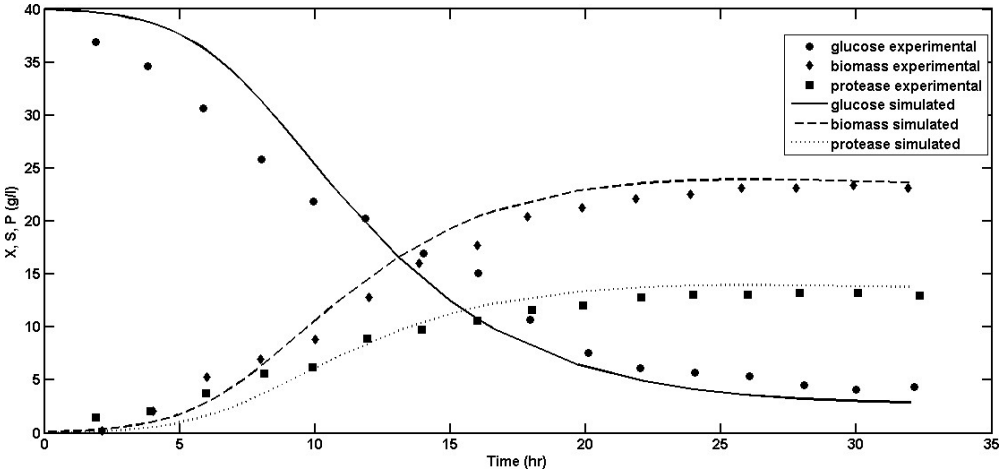

Figure 3 Multi-objective trade-off solutions for the MOOP case 1

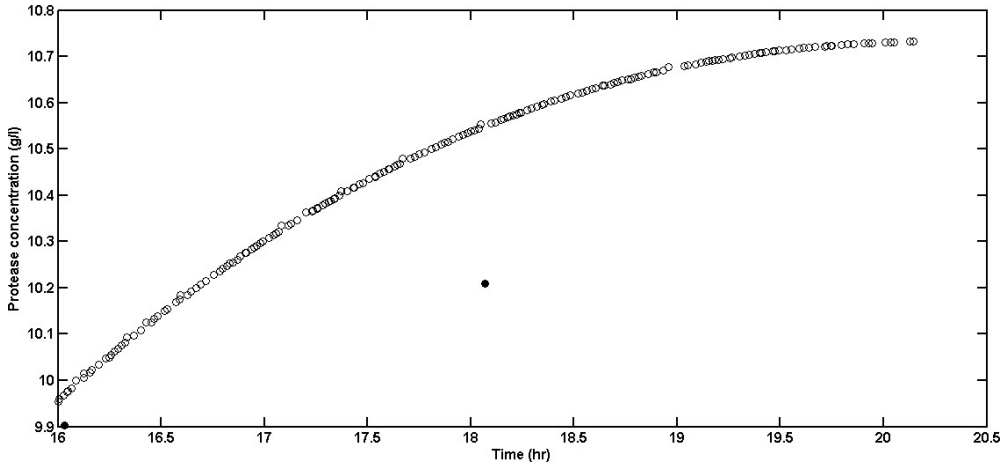

Figure 4 Optimised glucose addition patterns for the MOOP case 1

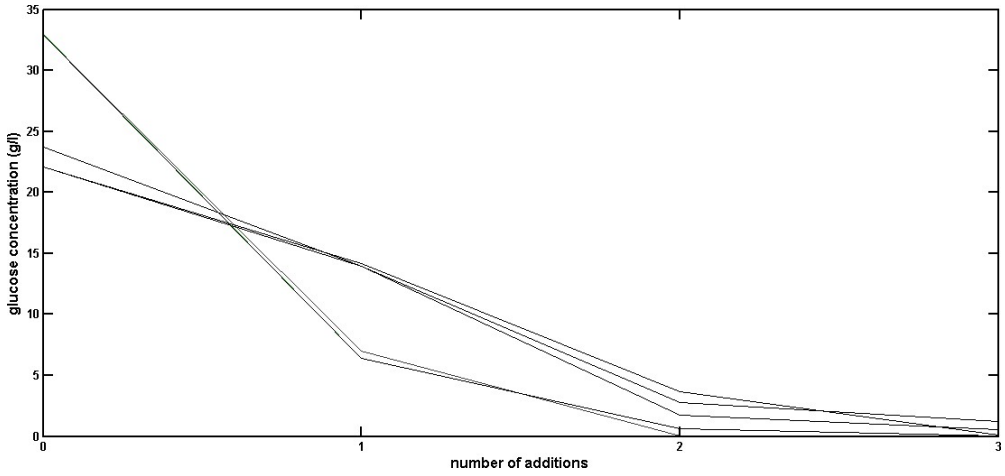

Figure 5 Multi-objective trade-off solutions for the MOOP case 2 (see online version for colours)

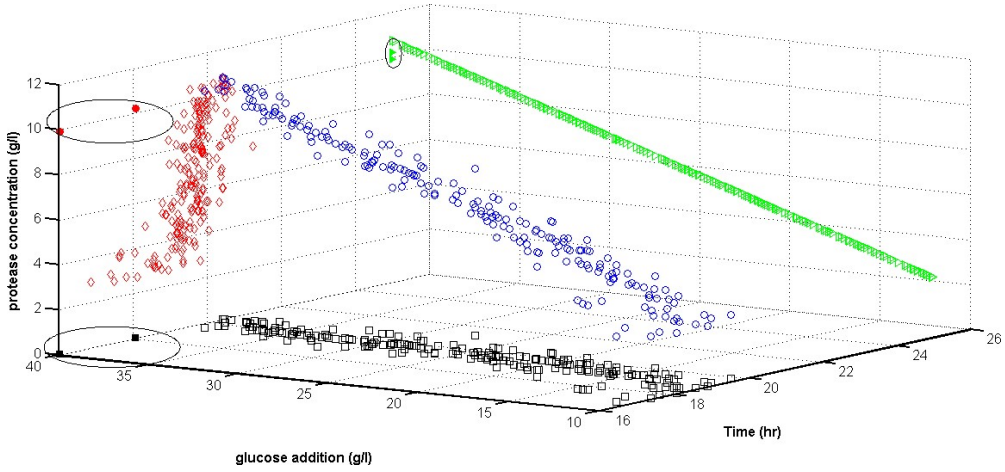

Figure 6 Optimised glucose addition patterns for the MOOP case 2 (see online version for colours)

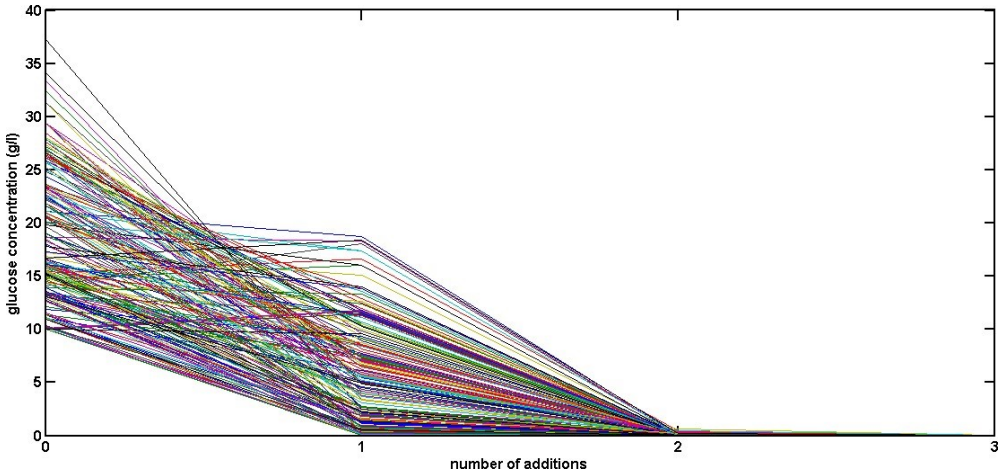

Figure 7 Multi-objective trade-off solutions for the MOOP case 3 (i.e., fed-batch)

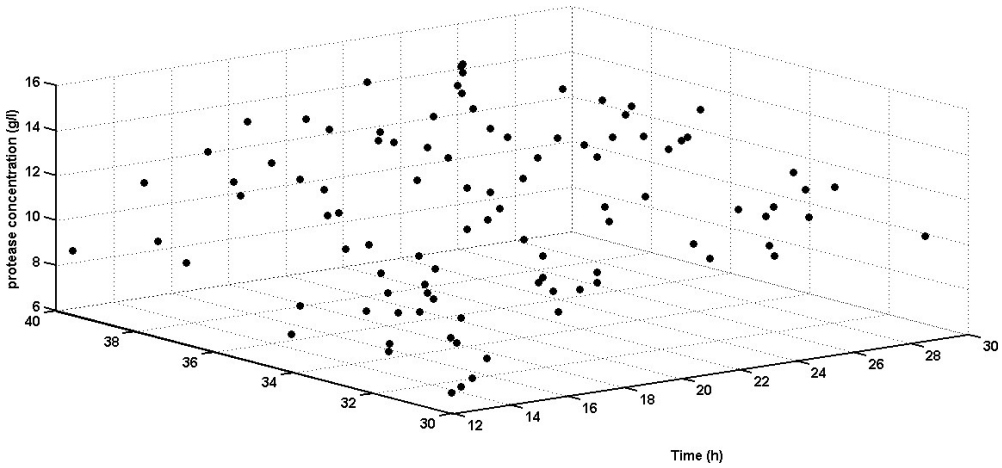

Table 4 Experimental batch comparison with semi batch addition of glucose (MOOP 1 and MOOP 2)

S. no.	*Fermentation time (hr)*	*Glucose concentration (g/l)*	*Protease concentration (g/l)*
Batch (Ghovvati et al., 2015)	18.1	40	10.2
MOOP 1	16.9	40	10.29
MOOP 1	18.17	40	10.7
MOOP 2	19.5	39.1	10.5
MOOP 2	20.5	38	10.2

Table 5 Experimental fed batch comparison with the MOOP 3

S. no.	*Fermentation time (hr)*	*Glucose concentration (g/l)*	*Glucose flow rate (l/h)*	*Protease concentration (g/l)*
Fed batch (Ghovvati et al., 2015)	24	40	0.01	13.13
Fed batch (Ghovvati et al., 2015)	26	40	0.01	13.35
MOOP 3	24.5	38.8	0.00803	13.8
MOOP 3	25.2	39.89	0.00802	14.2
MOOP 3	22.83	40	0.008	14.1

4 Conclusions

Multi-objective optimisation of semi-batch addition and fed-batch glucose addition for the alkaline protease production is studied in the present work to obtain the optimal process conditions. Minimisation of glucose addition and minimisation of fermentation time is attained along with the simultaneous maximisation of protease concentration without violating the constraints. Discrete glucose additions at equal intervals of time and fermentation time are taken as decision variables in the case of semi-batch addition of glucose. In the fed-batch case, same objective functions have been considered with glucose concentration, flow rate and fermentation time are considered as decision variables, which are bounded based on the experimental data. The major conclusions are in case of semi-batch glucose addition, there is a potential increasing of protease concentration in less fermentation time as compared to the batch data (e.g., almost 7% less in fermentation time with almost same protease concentration and around 6% improvement in protease concentration in almost same fermentation time). In the fed-batch addition of glucose also, productivity of protease also increased by 15% with the less glucose addition as compared to the fed-batch experimental data.

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Review of microplastic degradation: Understanding metagenomic approaches for microplastic degrading organisms

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ABSTRACT

Environmental problems caused by plastic pollution are among the most pressing issues of our time. In recent years, metagenomics has become a powerful tool for understanding the microbial communities responsible for plastic biodegradation. In this review, recent developments and trends in metagenomics are discussed, and a comprehensive overview of the metagenomic methodology, analysis, and comparison of plastic-degrading bacteria is provided. In addition, the environmental consequences of plastic degradation are discussed, such as the impact on soil, water, and air quality, as well as the potential health risks posed by ingesting and inhaling microplastics. Possible solutions to the plastic degradation problem, such as using biodegradable materials and implementing recycling programs, are also explained. This review highlights the potential impact of metagenomics on the development of sustainable solutions to plastic pollution.

1. Introduction

Plastic waste, especially microplastics, has become one of the biggest contributors to environmental and health hazards in the last decade. They are found dispersed throughout the planet, contaminating all natural environments, including marine, terrestrial, and water bodies, from the deepest part of the sea, the Mariana trench, to the highest Himalayan mountains [1,109]. These contaminations have led to significant microplastic accumulation and distribution of plastic to a higher level in the food chain, eventually making its way into the human body [2]. The United Nations has classified plastic pollution as one of the ten emerging environmental problems [3]. In 2015, more than six thousand metric tons of plastics were manufactured globally, of which 79% were accumulated in our environment, most notably in landfills. The growing worry surrounding the rise of plastic waste in ecosystems and its effects on organisms has prompted the development of biodegradable alternatives. Nonetheless, the extended degradation periods of these biodegradable plastics in natural environments indicate that they may still pose risks of ecological consequences. The precise impact of microplastics on organisms remains uncertain, particularly due to the utilization of particle concentrations in experimental exposures that greatly exceed those typically observed in natural ecosystems [116]. When this

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increasing rate of plastic production is paired with the current waste management system, by 2050, there will be about twice the amount of plastic waste in our environment [4]. To address this problem, an emphasis has been placed on using microorganisms and microbial enzymes to manage plastic waste sustainably. However, approximately 98% of microorganisms in microbial communities cannot be cultured under laboratory conditions, making the selection and characterization of countless plastic-degrading enzymes of microbial species arduous. With tremendous technological development and the collaboration of great minds in the field of bioinformatics and genome sequencing technologies, a new field has emerged, an amalgamation of the best of both worlds, metagenomics.

Metagenomics offers the solution to this microplastic crisis through next-generation sequencing (NGS), high throughput sequencing methods, shotgun metagenomics, and an array of modern omics, such as genomics, proteomics, and bioinformatics tools and software [110]. Analyzing metabolic pathways and microbial, phylogenetic, and functional diversity of uncultivable microbes using metagenomics provides crucial insights. The application of molecular biology and metagenomics has expanded our understanding and knowledge of the microbiome and its biological systems in polluted environments, allowing us to study microbial communities from highly contaminated sites [5,6]. This review article discusses the latest discoveries and trends in metagenomics, a comprehensive study on metagenomic methodology, analysis, and comparison of plastic-degrading microbes and their enzymes.

2. Elucidation of microplastics and their characteristics

2.1. Sources of microplastics

Plastics come in two varieties: large and small plastic waste less than 5 mm in size, known as microplastics. According to recent research, 8.3 billion tons of plastic have been generated worldwide since its created. An estimated 9% of this has been recycled, but the annual amount of plastic waste entering the ocean is between 4.8 and 12.7 million megatons. Considering these current estimations and efforts to quantify the issue, it is crucial to comprehend the connection between macro and microplastics [7]. Based on the annual garbage production per person, the proportion of plastic waste in that pollution and the proportion of poorly managed plastic waste that could end up in the ocean as plastic pollution indicate that there are more microplastics and larger plastics in the sea than the frequently stated average of 8 million metric tonnes [8]. The sources of microplastics considered here come from the roughly 300 million tons of plastics consumed worldwide. The primary uses are for plastic goods that start as pellets (85%), synthetic fabrics (11%), and synthetic rubber in tires (2%). The only losses that can be considered purposeful losses are losses from personal care products. Primary and secondary microplastics are the two types of microplastics that pollute the world's oceans. Primary microplastics are defined as plastics released directly into the environment as minute particles (Fig. 1). The first category of microplastics is purposefully added to water bodies. Whereas some secondary microplastics are the result of accidents during the synthesis, transportation, use, maintenance, or recycling of objects containing plastic through abrasion, weathering, or unintentional spills [9–11]. These fibers obtained through abrasion and fiber shedding, washing, etc., end up in the oceans. Significant numbers of these textile fibers have been discovered in both open-water and marine sediments through numerous in situ sampling studies [12]. The microplastics resulting from tires degradation are then dispersed by the wind or removed by rain into water bodies [108]. Marine coatings viz., Solid coatings, anticorrosive paint, and antifouling paint made from various plastics release microplastics during construction, maintenance, repair, and use (wear and tear) [13].

In personal care and cosmetic products, plastic microbeads cause plastic particles to be directly introduced into wastewater streams from residences, hotels, hospitals, and sporting venues such as beaches [14].

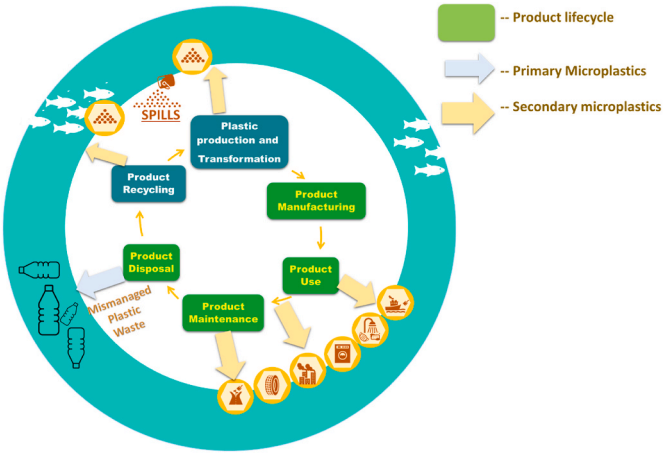

Fig. 1. Sources and distribution of various microplastics in the world's oceans.

(Fig. 2). City Dust is a catch-all name for a collection of nine causes recently identified in national assessments and most frequently seen in urban settings. City Dust includes losses from abrasion of infrastructure (home dust, city dust, artificial turfs, ports, and marinas, building coating), abrasion of objects (synthetic cooking utensils, synthetic shoe bottoms), abrasion of things, abrasive blasting, and deliberate pouring (detergents). These sources are combined because their separate contributions are negligible [15]. They eventually gather in gyres created by ocean currents. Estimates suggest that 93–268 kilotons of these microplastics floats in the waters [16]. Many microplastics will eventually accumulate in the deep sea and ultimately in food chains, as other types of microplastics, such as acrylic, are denser than saltwater and will most likely get deposited on the ocean bottom [17].

2.2. Types of microplastics

Microplastics are distinguished from larger plastic wastes, such as plastic bottles, containers, sheets, and waste plastic, by their size. Microplastics are currently classified into two types (Fig. 3). Any plastic pieces or particles that are 5.0 mm or smaller before entering the environment are considered the primary category of microplastics. Microfibers, beads, and plastic pellets used in clothing are a few examples (also known as nurdles). Secondary microplastics are created when larger plastic goods deteriorate in the environment due to normal weathering [18]. Secondary microplastics can come from various sources, including tea bags, fishing nets, water and soda bottles, plastic bags, microwave containers, and tire wear. Both types of contaminants are known to remain in the environment at high concentrations, especially in aquatic and marine ecosystems where they pollute the water. 35% of all ocean microplastics are made of textiles and apparel, mainly due to the normal evaporation of polyester, acrylic, or nylon garments. However, microplastics accumulate in the atmosphere and terrestrial ecosystems [19].

2.2.1. Primary microplastics

Small bits of plastic produced on purpose are known as primary microplastics. They are frequently discovered in cosmetics, facial cleaning products, and air-blasting technology. Their use as drug vectors in medicine has been described in some cases [20]. In exfoliating hand cleaners and facial scrubs, microplastic "scrubbers" have taken the role of naturally occurring substances such as powdered nut shells, oats, and pumice. For use in air blasting technology, primary microplastics have also been produced. Acrylic, melamine, or polyester microplastic scrubbers are fired at machinery, motors, and boat hulls to remove paint and rust (Gilbert, 2022). They are used repeatedly until their size decreases, and their cutting effectiveness is lost. These scrubbers usually

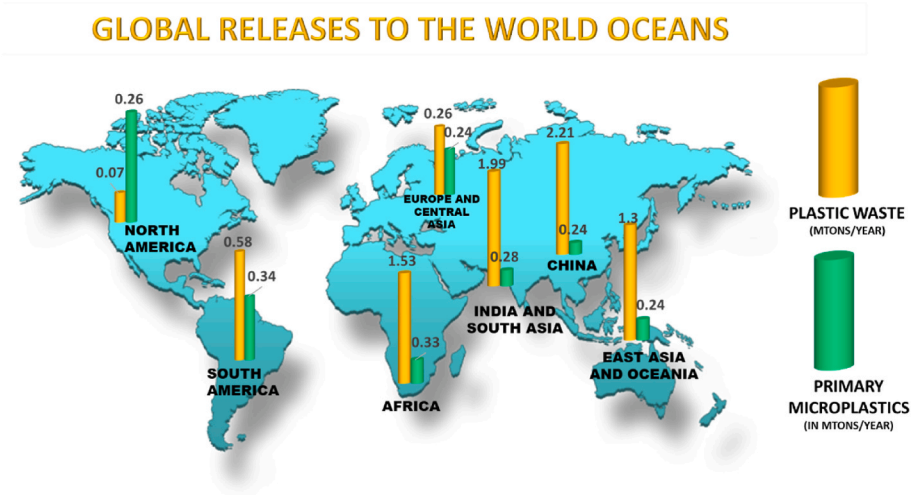

Fig. 2. Release of plastics, specifically primary microplastics, into the oceans by various parts of the world.

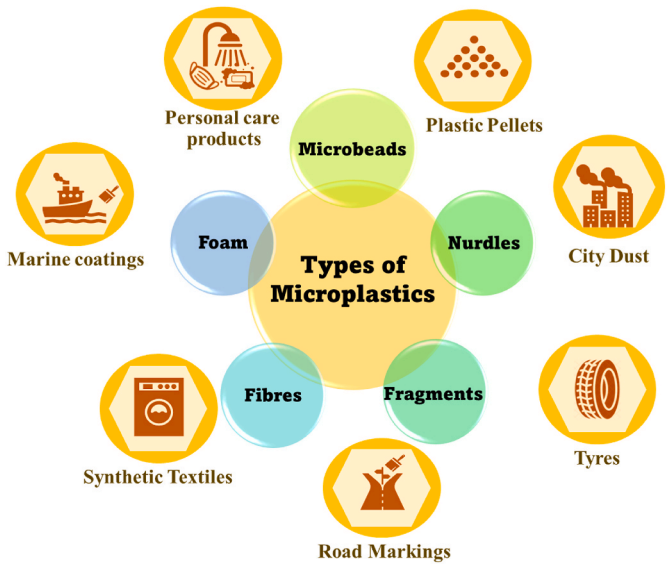

Fig. 3. Types of microplastics and where they are usually sourced from.

contain heavy metals, such as cadmium, chromium, and lead [21]. Although many businesses have pledged to cut back on microbead production, there are still plenty of bioplastic microbeads that degrade slowly, much like regular plastic [22].

2.2.2. Secondary microplastics

Secondary plastics are tiny fragments created as bigger pieces of plastic debris, both on land and at sea, break down [23]. A mixture of physical and biological means can gradually erode the structural integrity of plastic debris, and chemo-photodegradation processes, including photooxidation, are caused by sunlight exposure. Eventually, this can make the debris too small to be seen by the human eye. Fragmentation technique involves reducing large amounts of plastic material into significantly tiny pieces [24]. Although microplastics are believed to continue to break down and shrink in size, the smallest microplastic currently considered to have been found in the oceans has a diameter of 1.6 μm (6.31 in). The prevalence of microplastics in irregular forms indicates fragmentation is a significant source [25]. Some of them include Fibers [26,27], microbeads [28–30], polymer blends [113], Fragments [31], Nurdles [32–36], styrofoam [37–39]

2.3. Toxicity caused by microplastics

Microplastics, mainly in the range of 5 μm, are worldwide contaminants that are widely disseminated in the environment. They are constantly prevalent within human ecosystems. The scale of pollution, it is widespread and its long-term durability raises significant concerns about its impact on ecosystems, animals, and human health [40]. Microplastics have fatal impacts on the environment as they are abundantly distributed in the soil and aquatic ecosystems due to their minuscule particle size. They indirectly or directly affect plant life by clogging in plant parts such as roots, stems, or leaves, thus affecting their nutrient uptake. Toxic and hazardous chemicals are used during the process as additives to improve the properties of polymers and increase their useful life, thus transporting toxic chemicals across ecosystems [41,107]. The ecotoxicity of microplastics is seen not only in plants but also in animals. Microplastics are quickly taken up by the aquatic creatures and are transferred in the food chain to higher organisms, such as humans, thus becoming a source of concern for human health. Fish serve as one of the most integral biological models for assessing the toxicity of microplastics. Microplastic contamination of the aquatic ecosystem is one of the major concerns since they are easily ingested by the fauna in the waters and usually accumulate in their intestines. Several studies have proven the potential for microplastics to hinder reproduction capacity and cause fish organ failure [42,43].

At the apex of the food chain, humans are more vulnerable to microplastic contamination. Microplastics derived from the exhaust of gas and oil products tend to settle in household dust. They can be breathed due to their tiny size, and depending on individual sensitivity and particle qualities, they cause respiratory system lesions. Synthetic fibers of microplastics have been detected in human lungs by biopsies. Such airborne microplastics can cause injury or even death from chronic exposure due to their carcinogenic or mutagenic properties, potentially leading to cancer [44]. Microplastics have also been found to have a considerable influence on several regulatory enzymes, such as catalase, glutathione-*s*-transferase, and acetylcholinesterase [45]. Due to their ability to inhibit acetylcholinesterase, which results in an inflammatory reaction that may aid in the development of cancer, microplastics have also been shown to have neurotoxic effects. The interaction between humans and microplastics has been shown to affect cell function at the molecular level [46,47]. The inappropriate disposal of face masks worn during the COVID-19 pandemic contributes to the considerable amount of fibrous polypropylene microplastics found in non-woven fabrics. Again, this is another major factor responsible for the build-up of microplastics in air and water. Proper treatment of industrial effluents such as those of cosmetics, textiles, manufacturing, or other industries is

also crucial, as they tend to contain a high concentration of microplastics [48]. The impact of microplastics on living things may be broadly categorized into physical and chemical impacts. Physical effects include the size, structure, and concentration of microplastics, while chemical effects include their toxic traits [49].

3. Characterization of microplastic degrading microbes

3.1. Microbes and their enzyme action

The significance of microorganisms in plastic degradation in the natural environment is unclear. However, abiotic environmental degradation plays a significant role in the fragmentation of large plastic waste, leading to micro- and nano-plastic contamination. Recent reports suggest that several microorganisms can depolymerize artificial polymers in a laboratory environment [50,51]. Microbial biotechnology has frequently been suggested as a viable solution for sustainable plastic waste disposal, even if the actuality and potential of biotechnological recycling technologies are not yet clearly understood by scientific communities, plastic end users, and policymakers [52,111]. Microbial communities engaged in synthetic polymer degrading activities are a valuable source of enzymes. Biofilms that foul polyethylene terephthalate were reported to have undergone shotgun metagenomic sequencing by using ceramic, polyhydroxyalkanoate (PHA) and polyethylene terephthalate (PET) as the substrates at the sediment-water interface of a coastal lagoon [53]. PET plastic biofilms could not be distinguished from ceramic biofilm control. However, bioplastic biofilms of PHA could be identified because they were significantly enriched in phylogenetically diverse polyhydroxy butyrate (PHB) depolymerase and sulfate-reducing microorganisms (SRM). Here, it is seen how crucial the SRM of the plastisphere is to PHA biodegradation [53].

Numerous research studies have focused on the enzymatic breakdown of PET in the past ten years. The genome of the marine bacteria *Pseudomonas aestusnigri* included a unique PET hydrolyzing enzyme type IIa (PE-H), which was physically and functionally characterized. Amorphous PET was discovered to decompose at 30 °C via PE-H [54]. By rearranging the active site conformation in a Y250S variation, structural modeling and mutagenesis were used to gain new knowledge about the structural elements necessary for the effective degradation of polyester. This variant exhibit enhanced PET hydrolytic activity [105]. Although UV treatment significantly enhanced chain scissions at the surface layer of amorphous PET films, the resulting increase in surface crystallinity significantly decreased the effectiveness of enzymatic degradation [55]. The microbial metabolism of plastic monomers and additives will be a research focus on environmental degradation of plastic pollution and biotechnological plastic upcycling, i.e., the utilization of plastic hydrolysates as feedstocks for the microbial production of high-value chemicals. Engineered whole-cell catalysts have recently been identified to have a high potential for plastic degradation [56]. Depolymerases, which convert long-chain polymers into low molecular weight oligomers or monomers that can be taken up by microbial cells or broken down into CO_2, are secreted as the initial stage of the microbial degradation process. These depolymerization products could be utilized to manufacture high-value compounds via specific metabolic pathways, which align with the circular economy principle and could valorize plastic trash [57].

However, little is known about the depolymerase that aids in the decomposition of plastics. Therefore, future studies should focus on discovering additional depolymerase from microbes that degrade plastic. The efficiency of enzymatic breakdown must also be increased, which is a difficult task. On the one hand, the crystalline structures and cross-linking networks seen in the macromolecular aggregate structures of plastics prevent enzymatic breakdown [58]. These macromolecular aggregation formations may be disorganized and more amenable to enzymatic breakdown using physical pre-treatments like mechanical grinding and irradiation. However, directed evolution and rational protein engineering are needed to increase depolymerization activity and stability, increasing the efficiency of enzymatic degradation [59]. Although depolymerases could break down long-chain polymer molecules into smaller pieces (monomers or oligomers), cells would have utilized these tiny depolymerization by-products as metabolic feedstocks [60]. The comparative list of plastic-degrading enzymes and microbes is given in Table 1.

3.2. Mechanism of plastic degradation

3.2.1. Ideonella sakaiensis

A novel strain of bacteria called *Ideonella sakaiensis* 201-F6 can use PET as its main source of carbon. Two hydrolytic enzymes, namely mono (2-hydroxyethyl) terephthalate hydrolase (MHETase) and PET hydrolase (PETase) produced by *I. sakaiensis,* can break down PET into its monomeric components [67]. PET is transformed into mono-(2--hydroxyethyl) terephthalate (MHET) by the enzyme PETase, a consensus α/β hydrolase enzyme with a well-characterized structural fold. The second most necessary enzyme, MHETase, hydrolyzes MHET to produce PET byproducts of terephthalate (TPA) and ethylene glycol. Together, PETase and MHETase break down PET through MHET in two stages, producing simpler components required for a new cycle of PET synthesis (Fig. 4). While MHETase is necessary to destroy PET, its exact function is unclear. PETase effectively acts on PET in its crystalline state and at the optimal temperature [68].

3.2.2. Pseudomonas sp.

Pseudomonas sp. is a widespread and diverse microorganism genus with a total of 191 distinct species. As a result, they have a wide variety of properties, including plant growth factors, electroactivity, pathogenic activity, etc. Apart from these, the significant uses of *pseudomonas sps*. are bioremediation and plastic biodegradation. They produce simple enzymes to break down several types of polymers and aid in the degradation of PE, polystyrene (PS), polyurethane (PUR), and PET by employing primary enzymes such as hydrolase, alkene monooxygenase, esterase, lipase, and protease. The breakdown mechanism consists of two significant steps: the breakdown of macro-plastic into micro-plastic by extracellular enzymes such as depolymerase. This initial stage employs two distinct approaches, depending on the type of plastic: exo-attack (chain-terminal) for breaking smaller subunits and endo-attack (along the polymer chain) for molecular weight reduction. The tiny fragments of plastic traverse intracellular metabolic cycles such as the tricarboxylic acid (TCA) cycle and metabolic pathways, such as the catabolism pathway, in the second stage. Therefore, macroplastics would be completely decomposed into simpler compounds without toxicity [5,6].

PET is broken down into ethylene glycol (EG) and terephthalic acid (TPA) during the enzymatic degradation of polyethylene by Pseudomonas. Both products also gain new functional groups at the site of lysis. During hydrolysis, bis-(2-hydroxyethyl) terephthalate (BHET) and MHET are formed as intermediates that are converted into TPA and EG. The TPA is transported to the microbial cell by a TPA transporter, where it undergoes metabolic processes and is transformed into protocatechuic acid (PCA). PCA is metabolized in the TCA cycle. Likewise, EG is merged into the TCA cycle and biosynthesis process and metabolized. Enzymes such as hydrolase and polyethylene terephthalate are degraded by alkane hydroxylase (PET). The metabolic pathway consists of various phases, including oxidation, dehydrogenation, and breakage of carbon-carbon bonds, in the enzymatic degradation of PE. The PE is broken down into acetic acid, a new functional group, and then it is integrated into the TCA cycle. Metabolic hydrocarbon products of about 20 carbon atoms are transported directly into the microbial cell for the final breakdown. Hydrocarbons larger than 20 carbon atoms are metabolized outside the cell until through they can pass the microbial cell wall. And enzymes such as esterase and alkene monooxygenase will help in the

Table 1
List of plastic degrading microbes and enzymes.

Enzyme	Types of plastic	E.C number	Microorganism/s	Mechanism	Sample collection location	Reference
poly(3-hydroxyoctanoate) depolymerase	Polythene (PE)	EC 3.1.1.76	*Pseudomonas* sp., *Comamonas* sp	Hydrolysis	Gujrat, India	[5,6]
poly (ethylene terephthalate) hydrolase	Polyethylene Terephthalate (PET)	EC 3.1.1.101	*Fusarium oxysporum*	Hydrolysis	Gujrat, India	[5,6]
The cutinase-like enzyme (CLE)	PET	EC 3.1.1.74 (cutinase)	*Pseudozyma and Cryptococcus*	acid/base mechanism - acylation and deacylation processes	-	[61]
MHETase	PET	EC 3.1.1.102	*Ideonella sakaiensis*	Hydrolase	Sakai City, Japan	[62]
PET hydrolases	PET	EC 3.1.1.101	*Ideonella sakaiensis*	cleave internal ester bonds	Sakai City, Japan	[62]
Cut 190	PET	-	*Thermophilic actinomycetes*	Hydrolyze	-	[63]
T manganese peroxidase (MnP)	PE	EC 1.11.1.13	*Irpex lacteus*	Degradation of Polyethylene membrane	-	[64]
-	Polythene and other plastic	-	**Bacteria:** Pseudomonas sp., *Staphylococcus* sp., *Moraxella* sp., *Micrococcus* sp., *Streptococcus* sp. **Fungi:** *Aspergillus glaucus, Aspergillus niger*	-	Mangrove soil	[65]
-	Low-Density Polyethylene (LDPE)		**Bacteria:** *Bacillus* sp. *Pseudomonas* sp. *Streptococcus* sp. **Fungi:** *Aspergillus* sp. *Fusarium* sp		dumped soil, Chennai	[66]

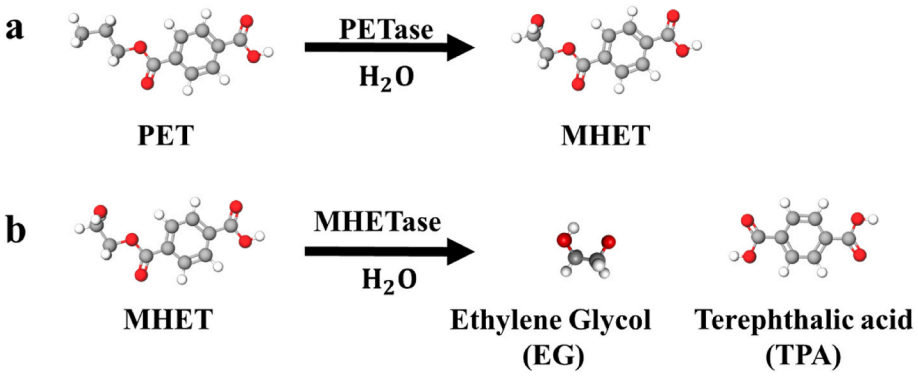

Fig. 4. PET degradation involving 2 different enzymes.

degradation of polystyrene [69].

3.3. Recent discoveries

Due to the possible risk, they pose to aquatic life and human health, as previously indicated, and their link with invasive microorganisms, microplastics in the ecosystem are currently a significant source of environmental concern [70]. Microplastics are ubiquitous in many environments, particularly aquatic and soil biomes [70–72]. Recent studies have revealed that microplastics are essential vectors for microorganisms that could form fully developed biofilms on this artificial substrate [71,72]. Microorganisms play a vital role in the breakdown of microplastics because they control nutrient cycling in the immediate environment, which links biotic and abiotic processes [73]. They have evolved enzymes to digest plastic particles into assimilable carbon sources, as they have unfortunately become prevalent in the environment [74]. The breakdown of microplastic particles is significantly influenced by abiotic environmental deterioration. However, research on the effects of bacteria on biotic circumstances is ongoing [6,75,76]. Environmental conditions like pH, temperature, etc., should also go hand in hand with the available microplastic-degrading microbes in the immediate circle [77].

Microplastic-associated biofilms are a prominent microplastic aggregation observed in the aquatic environment. Specific bacterial communities play an important role in the production of these biofilms. Microplastic biofilms selectively enhance certain pathogenic bacteria [70]. As we dig deeper into the processes, one fact is that biofilms have pros and cons. Both merge at the point where biofilms play an influential role in the development of microbial biocommunities [73]. In the absence of microbial activity, plastics slowly degrade, with half-lives ranging from hundreds to eons, depending on the polymeric material and the characteristics of the environment [74]. As mentioned above, microbial populations provide a rich source of enzymes that break down plastics. One such organism is pseudomonas, whose enzymes are extensively studied because of their ability, especially in the upcycling process [6,75]. The researchers found that a bacterial consortium significantly altered the surface topography and rheological properties of the degraded polyethylene surface by forming a biofilm. These findings showed that, like pure fungal cultures, bacterial consortia could accumulate as harmful biofilms on the surface of microplastics [77].

The degradation of plastic polymers is one of the most studied effects of microbial communities on microplastics. Recent research has

identified primary bacterial genera capable of dissolving poly (3-hydroxybutyrate-*co*-3-hydroxyhexanoate (PHBH) biofilms such as Alteromonadaceae and Burkholderiales. *Alcanivorax borkumensis* that grows in microplastic biofilms appeared significant in the degradation process of low-density polyethylene. Furthermore, it has been shown that Erythrobacter species in microplastic biofilms break down hydrocarbons [70]. According to a recent study, aquatic bacteria have adapted to plastics as a surface for colonization and may even break them down. For instance, numerous types of plastic, including macro- and microplastics, have been found to contain Erythrobacteraceae, a common aquatic bacterium that colonizes plastic [73]. PET plastics are one of the most common and widely used materials. In its macro or microform, PET degradation or hydrolysis is prompted by one of the most efficient enzymes, named IsPETase, isolated from *Ideonella sakaiensis*. In recent years, much research has been aimed at improving the stability and efficacy of IsPETase. Numerous recent reports have detailed point mutations that have been systematically engineered to make IsPETase a better fit for industrial use for the degradation of microplastics [74]. Another organism, *Pseudomonas aestusnigri,* with its enzyme PE-H at 30 °C was found to break down amorphous PET. A Y250S variant was created using structural modeling and mutagenesis due to the rearrangement of the active site conformation. This variant showed improved PET hydrolytic activity and novel structural qualities required for efficient polyester degradation [6,75].

An enzyme or a couple of enzymes with the capability of degradation are not enough for the enormous amount of microplastic that must be washed off from the biosystem. To at least achieve the primary goal of degrading the microplastics, the combination of different enzymes from a particular type of organism is highly preferred, i.e., a bacterial, fungal, etc. This application could eliminate toxicity or toxic metabolites formed during degradation [77]. In general, the composition of the microbial community and essential microbial respiratory processes of the bacteria are influenced by the redox environment. As a result, microbes can interact actively with microplastics, coupling accessible redox mediators to polymer breakdown [73]. As always said, no matter the numerous mechanisms and biodegradation processes, curbing the actual problem is to lessening the use of any type of plastic or at least decrease the habit of inconsiderable disposal of plastic waste [71,72]. Recent studies indicate that fish, crabs, and other aquatic creatures readily consume microplastics. This, in turn, leads to bio amplification if plastics enter the food chain [70]. Another critical research to improve sustainability in food and agriculture is innovation in the performance and economics of bioderived and biodegradable plastics that avoid microplastic accumulation. It is strongly recommended that the food and agriculture sectors invest heavily in biodegradation technology to reduce microplastics in food and agricultural goods [74].

4. Metagenomic analysis

Various microbial communities can be drawn out, which, possibly, with the help of the enzymes they manufacture, contribute to the breakdown of microplastics. Not all enzymes produced by the microbial population are efficient enough to participate in the degradation process. To understand the nature of the microbial community and anticipate its ability to participate in in-situ biodegradation, a metagenomic study of the microbial population participating in plastic biodegradation is recommended as a solution to this problem [78]. Detailed metagenomic analysis of microbiomes and mining of associated genes and enzymes involved in biodegradation is now possible because of advances in bioinformatics and sequencing methods. Therefore, metagenomics could be a valuable method to discover effective plastic-degrading genes and enzymes in uncultivable microbial populations [104,112]. The metagenomic analysis evaluated the genomic capabilities of aquatic plastic biofilms, as well as the levels of protein expression [79]. As the previous topics suggest, biofilms are one of the peculiar properties encountered in the process of degradation of microplastics. The composition or characterization of these biofilms depends on the strata or atmospheric level at which they are formed. This can be proved by shotgun metagenomic studies. At the sediment-water interface of a coastal lagoon, biofilms that break down plastic and microcosms made of bioplastic were shotgun metagenomic sequenced. According to a study conducted by Pinnell and Turner in 2019, plastic biofilms showed the same community composition as the ceramic biofilm control. This finding suggests that plastic-degrading microorganisms can be investigated through metagenetic studies. By examining the microbial community within the “plastisphere” and identifying novel genes or enzymes involved in the degradation of various polymers, we can uncover a vast and unexplored microbial gene pool. This approach holds great potential for biotechnological applications and further advancement in the field of valorization, as highlighted by Kirstein et al. [84].

According to environmental microbiologists, only 2% of entire microbiomes can be grown in the research lab, leaving a large fraction of uncultured fungus, bacteria, and other microorganisms undiscovered [80]. New developments in computational tools and next-generation sequencing techniques have allowed the parallel investigation of many biological samples by processing millions of DNA/RNA fragments [81]. The metagenomic analysis of any microbial biosystem can be broadly divided into the following ways, irrespective of the state., (a) structural metagenomic approach, (b) functional metagenomic approach, and comparative metagenomic approach [82].

4.1. Structural metagenomic approach

The primary goal of a structural metagenomic approach is to reveal the microbial community structure of any specific ecosystem by sequencing environmental samples. This will primarily provide the taxonomic identity of the microbial community in a culture-independent manner. However, it may also be used to investigate other aspects, such as identifying novel genes, predicting gene functions, and involving genes in various metabolic processes. Additionally, it will help establish connections between community members’ preferences for the environment. Assigning minor or significant geo-ecological functions to microbiomes in the evolution of the community structure also provides information about the microbial population dynamics of a particular ecosystem at various spatial and temporal scales [78].

4.2. Functional metagenomic approach

Functional metagenomics helps determine the expression of a gene based on its sequencing or information about the structure. Beginning with the extraction of DNA from ambient sources, it predicts the likely required genes from a metagenome library and then moves on to heterologous expression for activity-based screening and functional validation. As a result, functional metagenomics is utilized in conjunction with sequence-based structural metagenomics to aid gene identification from the massive metagenomic database [78,83].

4.3. Comparative metagenomic approach

Additionally, a comparative metagenomic analysis of the various “plastispheres” of broad ecosystems could help identify the core microbial community, or the microorganisms that consistently persist over time to carry out a significant portion of plastic degradation and appear to be common in “plastispheres” across various geographical locations. Methods of adaptability, viability, and survival in their varied biological contexts (from marine to terrestrial) with the ability to degrade plastic could also be studied. Therefore, it is feasible to accelerate the degradation process by altering the microbial community and its metabolic processes in the plastisphere [78,84].

4.4. Analysis of microbial community structures through metagenomics

Using the three techniques above, the community structure of a microbiome can be deciphered. Community structure, physiochemical structure, and habitats, among others, are known to vary among microbial community belonging to similar ecological communities. The microbial population associated with plastics has a different makeup and evolves as the plastic deteriorates. According to reports, the varied species in the "specific" assemblage are congruent with types of plastic and can be recognized from other communities [78]. There are mainly two types of colonizers attributed to biofilm formation, i.e. primary colonizers and secondary colonizers. After 24–36 h, depending on the type of substrate and habitats, the buildup of primary colonizers modifies the subtratum, trying to make it favorable for further colonization by various secondary colonizers. Microorganisms arrive later in the biofilm formation process and may have unique features, indicating they are secondary colonizers. The structure of the microbial community evolves with time, and the relative proportions of secondary colonizers increase. The evolution of biofilm formation is represented by this progressive transition in community structure from primary to secondary colonizers over the duration [85].

Due to this variation in plastisphere characterization, metagenomic studies are limited to the structural analysis of the microbiome [84]. Although it helps the discovery of new microbial species, quantification of their abundance in the local microbial niche, and quantification of their rarity, the classification of these species into "core" to "specific" and "rare" species depends on their richness and specificity. Their functional involvement in the breakdown of polymers is still unknown. Purohit et al. [78] illustrated that some enzymes that can be used for the degradation of microplastics on the laboratory scale are not always suitable for performing the exact mechanism in a natural environment. For example, PETase hydrolysis is one of the most frequently used on disposed PET plastics in marine environments. A different form of the same enzyme can be obtained from *Ideonella sakaiensis* in iPETase. This enzyme is not suitable for the degradation of plastics in an aquatic environment. Researchers are now using a functional metagenomic method to address this problem by harvesting PET hydrolase homologs from various microbial sources. PET hydrolases are expected to be widely distributed in marine and terrestrial metagenomes based on conserved amino acids and can be exploited using various genetic engineering techniques for suitable modifications to the desired organism [78,83].

4.5. Deciphering a possible explication from metagenomic studies

The key benefit of metagenomic analysis is its rapid and effective means of highlighting the structural and functional importance of the relevant microbial niche [82]. A viable solution is developed based on all the data offered by metagenomics to meet the requirements of the microplastic breakdown process (Fig. 5). This answer can be divided into two categories, namely (a) modification of the external environment-microbial community and (b) modification of the internal cell primordia – genetic manipulation.

The first category describes the modification of the environment in which the microbial bio community is present. These modifications can be applied using various chemicals or molecular methods or by introducing different sources of nutrition to the microorganisms in the community. This modification will eventually enhance the structure of the microbial component, resulting in better degradation of plastics. The second describes the modification of genes or enzymes using microorganisms that are tailored to fit the need. In this way, the functional characterization of a particular microbial community can be altered by delivering the genes of interest into the organism's genome [78]. As a result, we can conclude that the development of metagenomic methods aids in the fabrication of proteins with enhanced characteristics, as well as the discovery of novel genes and the functional investigation of those

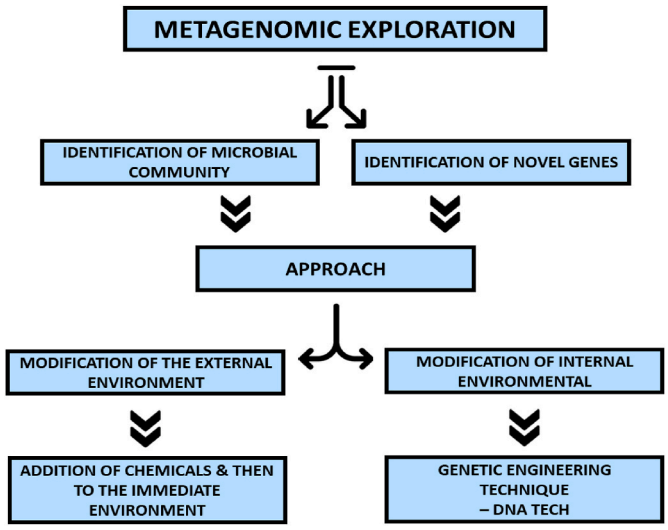

Fig. 5. Deciphering a possible explication of metagenomic study's.

genes through heterologous expression. To provide specialized solutions to problems, the biotechnological potential of metagenomics is emphasized, making it possible to obtain increasingly important information about the microbial world in order to address a range of societal and environmental problems.

4.6. Metagenomic analysis of plastic degrading enzymes in landfills

Around 21–42% of the plastic generated worldwide is reportedly disposed of in landfills [86]. Gaytán et al. [106], in their study on the polyurethane and xenobiotic biodegradation procedure and the evaluation of the product, revealed that the BP8 community breaks down various groups and bonds, including ester bonds, C-C bonds, aromatic recalcitrant urethanes, and ether groups. This was accomplished using oxidation and hydrolysis processes in all types of copolymer segments. The five genomes reconstructed using metagenomic analysis based on proximity ligation contained three genomes from the novel species. The identification of genes associated with different enzymes, such as putative enzymes and metabolic processes responsible for the biodegradative function of the BP8 population for additives and copolymers, was found in the metagenome. This work is the first to identify possible genes for microbial populations collected from landfills and water polyurethane dispersions systems that perform biodegradative processes. They also present viable solutions for the contaminations caused by xenobiotics and PU. Phylogenetic analysis identified well-supported clades for Paracoccus, Chryseobacterium, Parapedobacter, and Ochrobactrum intermedium, all of which are members of the Microbacteriaceae family.

Similarly, Kumar et al. [5,6] conducted a metagenomic analysis of the solid waste disposal site in Gujarat, India. Their study predicted thirty phyla, fifty-eight classes, 125 orders, 278 families, and 2468 distinct species. The most prevalent species in the soil and compost samples were Proteobacteria, Bacteroidetes, Firmicutes, and Actinobacteria. However, the leachate samples exhibited a predominance of phyla Firmicutes (54.24%), Actinobacteria (43.67%), and Proteobacteria (1.02%). The study also identified probable genes related to the decomposition of other plastics, such as PE, PS, and PET. Their research found a link between numerous gene sources actively participating in plastic waste biodegradation at landfill sites and the structured microbial community. Through the analysis of the Kyoto Encyclopedia of Genes and Genomes (KEGG), they found a total of 11 significant metabolic pathways, out of which the top five metabolic pathways were carbohydrate metabolism (21.92%), lipid metabolism (6.95%), energy metabolism (14.53%), amino acid metabolism (18.12%), and

metabolism of cofactors and vitamins (10.34%). According to the KEGG annotations, in parallel to the above, only about 10.82% of the metabolic pathways predicted the general function, while 9.62% predicted amino acid transport and metabolism, 8.45% predicted ribosomal translation structure, and 7.67% indicated energy generation and conversion.

Sonnendecker et al. [91] studied PET plastic recycling by polyester hydrolase enzyme using metagenomic analysis at compost sites in Leipzig, Germany. Their study found that amorphous PET films are entirely hydrolyzed by polyester hydrolase PHL7, which was isolated from a compost metagenome. This enzyme releases 91 mg of terephthalic acid every hour. The PET film deterioration rates, measured by vertical scanning interferometry, were 6.8 μm h^{-1}. According to structural studies, leucine at position 210 is crucial for PHL7's robust PET-hydrolyzing activity in any energy-intensive pre-treatments; 0.6 mg_{enzyme} $gPET^{-1}$ destroys the post-consumer thermo-form PET packaging completely in 24 h at 70 °C in an aqueous buffer. Polyester hydrolases can function as catalysts in environmentally friendly, sustainable PET recycling processes by recovering terephthalic acid from the enzymatic hydrolysate and using it to create virgin PET. In a study conducted by Zrimec et al. [115], the microbial potential of plastic degradation concerning the trends in plastic pollution, they developed a list of approximately thirty thousand non-redundant homologs enzymes that could break down ten distinct kinds of plastic. They also discovered that the quantity of enzymes in the ocean rises with distance downwards. After collecting further pollution measurements, they also discovered that the abundance of enzymes in soil and ocean ecosystems was strongly correlated with changes in marine and nation-specific plastic pollution. Thakur et al. [87] conducted a metagenomic study to search for novel enzymes in Delhi, India, solid waste landfills. They found that, based on operational taxonomic unit (OTUs), Proteobacteria were the most prevalent species in all samples, followed by Actinobacteria, Firmicutes, Bacteriodetes, and Chlorofexi. Verrucomicrobia and Acidobacteria were among the other relatively dominating species that were highly prevalent in other samples, while the Parcubacteria and Tenericutes species were enriched in other samples. It was discovered that the average percentage of the phylum proteobacteria in all samples was 40.54%, followed by Actinobacteria, the second dominating phylum, and firmicutes, the third most prevalent. They speculated that members of the phylum Firmicutes play a significant role in the breakdown of cellulose in landfills and are one of the most critical bio-degraders of biomass there. Other phyla included Chlorofexi and Bacteroidetes. Iodidimonas, a rare genus, was detected only in sample V. In contrast, Flavifexus was present only in sample T. A different uncommon species from the phylum Bacteroidetes, Patricia, was discovered in samples V and T.

4.7. Metagenomic analysis of plastic degrading enzymes in marine

Anthropogenic activities and other causes have strained coastal and marine ecosystems for many years. The environment is being physically destroyed and polluted. Due to unsustainable development and building operations, one of the severe risks humans have posed to marine and coastal systems is the build-up of debris or litter. As a result of poor garbage disposal, the ocean's surface is covered with five trillion bits of floating plastic waste [88].

Pinnell et al. [53] conducted a study on the Benthic microbial community in the marine environment in Texas, USA, and found that Proteobacteria Operational taxonomic units of Proteobacteria (OTU) were the most prevalent across the four types of communities at the phylum level of all operational taxonomic units in saltwater, pottery, PET, and PHA samples, respectively. Cyanobacteria were the next most prevalent phylum in the saltwater community (25%). The PHA biofilm communities were the only ones where Chloroflexi (4%), Spirochaetes (4%), and Firmicutes (2%) were present among the most numerous phyla. Synechococcus and Prochlorococcus, the two genera of Cyanobacteria, made up almost 20% of all operational taxonomic units in the seawater community but only accounted for 1% of the three biofilm communities. In the PET and ceramic biofilm communities, members of the uncultured genera Desulfobacteraceae, Rhodobacteraceae, and Flammeovirgaceae were among the five most prevalent genera, accounting for about 20% of all OTUs. 25% of all OTUs in the PHA biofilm were represented by three genera of Desulfobacteraceae and one genera of Desulfobulbaceae that were not cultivated, highlighting the dominance of SRM in that community. Six high-quality metagenome-assembled genomes were recovered from the co-assembled PHA biofilm metagenomes. The first genomes assembled with identified metagenomes were Desulfovibrio, the Desulfobacteraceae family, the Desulfobulbaceae family, the Spirochaetaceae family, and the Gammaproteobacteria order.

Bryant et al. [89] conducted a study on microbial diversity and activity in the North Pacific Subtropical Gyre. To ascertain the metabolic activities of the microplastic, the authors employed the Chlorophyll analysis approach in conjunction with a few additional methods and discovered that heterotrophic and photosynthetic microorganisms were attracted to plastic garbage. Additionally, they discovered that multispecies microbial biofilms, including pennate diatoms and coccus, rod and spiral-shaped cells, were connected to the frontal membranes of bryozoans. On bryozoan surfaces, bacteria with long filaments and prostheses were also observed. Similar cell morphologies could be visible on plastic particle surfaces, with some cells nesting inside the pores of the material. The Rhodobacteraceae and Cyanobacteria subsection III family I group, which includes Phormidium and Leptolyngbya, were the most common microbial families in both tests, according to their research. Additionally, Hyphomonadaceae, Flavobacteraceae, Saprospiraceae, and Flammeovirgaceae regularly contributed to microbial plastic communities. Vibrionaceae, on the other hand, was rare in the samples from their analysis but quite frequent in one sample from the Atlantic.

Similarly, Meyer-Cifuentes et al. [90] researched the biodegradation of plastic by marine microbial populations. They conducted three separate experiments: detection of CO_2 synthesis and breakdown products, meta-omic analysis of various microorganisms, and identification of potential genes and proteins. A varied community was discovered by assembling and profiling metagenome, mainly made up of Alphaproteobacteria, Gammaproteobacteria, Flavobacteria, and Actinobacteria, albeit in smaller quantities. Throughout the duration of the time series experiment, the abundance profiles remained constant. In this experiment, the six most prevalent bins were three from the Rhodobacteraceae family, including two Pseudooceanicola spp., one unidentified Rhodobacteraceae bacteria, and one each from Marinobacter, Aequorivita, and Micavibrionaceae. Six orthologues of the three PETases were discovered, sakaiensis PETase (A0A0K8P6T7, GAP38373) (IsPETase), leaf compost cutinase (AEV21261.1) and Thermobifida fusca cutinase (ADV92528.1). Furthermore, four possible enzymes resemble MHETases and can break down polymers and waste products left behind by those breakdowns. Our findings demonstrate that only a few genes and organisms are active during biodegradation, although many can carry out each stage of degradation (Table 2)

5. Case studies

In a study carried out to establish and validate a suitable technique to extract and quantify microplastics of varying sizes and forms from sewage sludge samples, it was found that over 190 days, soils containing sludge with the highest microplastic concentration produced the least biomass and no mature fruits were borne. Several factors, such as soil humidity and temperature, precipitation, and air temperature, influence biomass production, the availability of soil nutrients being the most critical among them. Both surplus and deficit nutrients adversely affect biomass and tomato production [92,93]. Overall, alterations in the soil's C: N ratio, which changed the availability of nutrients, significantly

Table 2
Studies done in metagenomic analysis of plastic-degrading microbes and their enzymes.

Aim of the study	Type of plastic	Ecosystem	Phylum/Family	Discovery	Location of sampling	Reference
Degradation of Recalcitrant Polyurethane and Xenobiotic.	PU, PE-PU-A, N-methyl pyrrolidone, isopropanol and glycol ethers	Landfills	Microbacteriaceae, Paracoccus, Chryseobacterium, Parapedobacter, and Ochrobactrum intermedium.	BP8 community functions & three novel species metagenome.	Nezahualcóyotl Estado de México, México.	Gaytán et al. [106]
Metagenomic analysis of the solid waste disposal site.	Soil waste compost	Landfills	Proteobacteria, Bacteroidetes, Firmicutes, and Actinobacteria. Firmicutes, Actinobacteria, and Proteobacteria.	2468 distinct species & eleven significant metabolic pathways.	Gujarat, India.	Kumar et al. [5, 6])
Use of metagenomic polyester hydrolase to recycle plastic.	PET	Landfills	-	PHL7's role in plastic degradation.	Leipzig, Germany.	Sonnendecker et al. [91]
Relation between global plastic degrading microbial populations and trends in pollution.	Plastic (10) PVA, PLA, PU, PHB, PBS, PET, PBAT, PE, PEG, PHO Additive (4) Phthalate PA, DBP, TP,	Landfills and marine	Acidobacteriota, Actinobacteriota, Alphaproteobacteria, Bacteroidota, Bdellovibrionota, Chloroflexota, Desulfobacterota, Gammaproteobacteria, Gemmatimonadota, Latescibacterota, Marinisomatota, Myxococcota, Planctomycetota, Poribacteria, Spirochaetota, Thermoplasmatota, and Verrucomicrobiota.	30,000 non-redundant enzyme homologs.	169 samples from 38 countries.	Zrimec et al. [115]
Using metagenomics for finding new microbial enzymes in the solid-waste dump.	compost	Landfills	Proteobacteria, Actinobacteria, Firmicutes, Bacteriodetes, and Chlorofexi. Verrucomicrobia and Acidobacteri. Parcubacteria and Tenericutes.	Novel enzymes, and bacterial Communities.	Delhi, India.	Thakur et al. [87]
Shotgun metagenomic analysis of microbes acting on Coastal plastic and bioplastic.	biofilms of plastic and bioplastic	Marine	Proteobacteria, cyanobacteria, Chloroflexi, Spirochaetes, and Firmicutes.	novel species of Desulfovibrio, Desulfobacteraceae, and Desulfobulbaceae	Texas, USA.	Pinnell et al [53]
Study the diversity of the microbial population and their activities in North Pacific Gyre.	Microplastic	Marine	Rhodobacteraceae, Cyanobacteria, Phormidium, and Leptolyngbya. Hyphomonadaceae, Flavobacteraceae, Saprospiraceae, Flammeovirgaceae, and Vibrionaceae.	che genes, secretion system genes, and nifH genes.	North Atlantic Subtropical Gyre.	Bryant et al. [89]
Microbial symbiotic biodegradation of aromatic copolyester.	aromatic-aliphatic copolyester	Marine	Alphaproteobacteria, Gammaproteobacteria, Flavobacteria, and Actinobacteria. Rhodobacteraceae, Pseudooceanicola spp., Marinobacter, Aequorivita, and Micavibrionaceae.	6 PETase-like enzymes and 4 MHETase-like enzymes.	Helgoland, Germany. Athens, Greece. Elba, Italy	Meyer-Cifuentes et al. [90]

influenced the growth rate [94].

Microplastic contamination occurs not only in the soil but also in water bodies and in more significant proportions. Microplastics were found in every sample of water tested, including drinking water, according to research to determine the number of microplastic particles in freshwater and drinking water. Microplastics of 10 μm size were the most prevalent in both treated and untreated water. Even particles down to the size of 1 μm were also identified as polyethylene. PET, PP and PE formed the majority of 12 other microplastic materials that were obtained. However, raw water was shown to have a more significant proportion of microplastics than treated water [95]. The quantification of microplastics was also carried out for 16 months near the Ofanto River in the Apulia region of southeast Italy. Black flakes and transparent fragments of microplastics were found at various concentrations. Their origin was mostly found to be land-based [96]. The effects of microplastics and other pollutants of various types in the aquatic ecosystem caused more significant damage to zebrafish than the contaminants were present alone, according to an investigation in which environmental circumstances were recreated in the laboratory. This combination resulted in adverse failure of the fish's internal organs [42,43]. In another similar study, the impacts of microplastics were studied at actual ambient levels where the microplastics were detected in the gills, intestines, and life of Oryzias melastigma, also called the marine medaka. These microplastics caused structural damage and increased oxidative stress in the tissues that made up the vital organs. The fecundity of the fish was also markedly reduced [9,10]. Similar toxicity effects were also observed in other aquatic beings, such as amphipods, crustaceans, and aquatic gastropods. Fish and other underwater organisms in areas that support mangrove growth serve as a food source for a large population. Recently, further research has been conducted to detect microplastic traces in these organisms. Among the other polymers, polycarbonates, and polystyrenes were detected in the highest

concentrations [97]. The mudskipper fish from India's Ulhas River estuary provided another set of findings. These fish are selective feeders, so micro-sized plastic particles were easily ingested. In contrast, the larger ones were inhibited, leading to a more significant accumulation of these microplastics in the gills. Microplastics were also found to accumulate in other fishes, such as long-tailed tuna (*Thunnus tonnggol*) and Sawtooth barracuda (*Sphyraena putnamiae*) [97].

Microplastics were also accumulated in several regions of the aquatic plant *Utricularia Vulgaris,* such as the leaves, shoots, and bladders of the plant. This accumulation elevates the antioxidative enzyme activity of the plant, thus increasing oxidative stress that leads to damage to plant parts [98]. Microplastics were detected in the roots of *Vicia faba* using laser confocal scanning electron microscopy, and a comparable impact of microplastics was also identified there [99]. A study conducted in the 11 most secluded and protected regions of the United States reported the accumulation of primary and secondary microplastics in dry and wet atmospheric depositions. A total of 339 samples (wet - 263, dry −103) were taken and most of these particles were synthetic microfibers of size 20 to approximately 3 mm and other particles of size 4–188 mm [100]. Microplastics have also been found in air debris collected from many places [101,102]. The build-up of minute plastic particles in arable soils, which might have unanticipated effects on soil quality and output, is now causing significant concern. Four agricultural areas and a buffer zone of the riparian forest at Dian Lake in southern China were investigated for the prevalence and distribution of plastic particles in mixed soil fractions. In 50 soil samples, plastic particles were discovered in sizes ranging from 0.05 to 1 mm. Compared to buffer soil, the concentration of microplastics in vegetable soil was greater, indicating the use of soil additives [103]. Microplastics have also been found consistently in several of China's inland water systems. It was discovered that most of these had secondary origins[114]. A significant accumulation of microplastics was also detected in one of the most critical drinking water sources of China's Nanning city, both in the surface waters and in the sediments. Polypropylene and polyethylene were detected at the highest concentrations [71,72].

6. Conclusions

Microplastic pollution continues to pose a significant challenge in the fields of environmental engineering, ecology, and materials science. Exploring the biodegradation of microplastics through research can enhance our understanding of how to mitigate their presence in the environment and develop innovative technologies to combat pollution. The efficient degradation of microplastics by microbes using various enzymes highlights the importance of studying enzyme activities, particularly in the context of micropollutants, which have emerged as a major environmental concern. Applying such knowledge on a broader scale could lead to the development of more effective degradation mechanisms for heavily polluted areas facing multiple pollution problems. In-depth comparative studies focusing on identifying the most suitable enzymes for microplastic degradation are crucial, particularly when dealing with high volumes of micropollutants. While traditional methods are valuable for unlocking the potential of different microorganisms, interdisciplinary approaches like structural or functional metagenomics hold significant importance, especially in the face of escalating environmental pollution. By incorporating these approaches into projects, concrete conclusions can be drawn within a short timeframe. In the future, it is essential to extend these techniques to encompass the larger ecosystems that serve as primary carriers of microplastics.

Thoroughly investigating microplastics, including their distribution, associated risks, spatial dispersion, temporal trends, and the interplay of external factors with microbe behavior using chemical and visual cues, is crucial. Understanding the health risks posed by microplastics and other chemical pollutants in the environment is also of paramount importance. Furthermore, the development of beneficial microbial agents is necessary to effectively reduce microplastic pollution. This comprehensive review provides valuable insights into the metagenomics of microplastic-degrading organisms, shedding light on their environmental roles. However, further investigations are still needed to explore the use of metagenomic approaches for identifying and characterizing microplastic-degrading organisms, as well as understanding the environmental factors influencing their growth and activity. Continued research in this area will yield useful insights and aid in the development of effective strategies to combat plastic pollution.

Authors contributions

All authors had full access to all the contents of the review paper and take responsibility for the integrity and accuracy of the text and analysis. Study concept and design: CNR. Acquisition of data: KVSSNM, AM, JCJR and ACVS. Analysis and interpretation of data: KVSSNM, AM, JCJR, ACVS,VP and CNR. Drafting of the manuscript: KVSSNM, AM, JCJR, ACVS, BM, YR, SKM, PK,VP,MH and CNR. Overall supervision: CNR, FB, MH.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Review

Valorization of agro-industrial biowaste to biomaterials: An innovative circular bioeconomy approach

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ABSTRACT

Population growth and increased food demand have increased global waste. Converting biowaste into biomaterials has been the subject of extensive research, and various strategies have been investigated. Microorganisms can ferment a large amount of useable carbon in biowaste from the food and agricultural industries to produce valuable goods. Those who advocate for a "circular bioeconomy" aim to establish a system that eliminates waste by recycling and reusing its components. Various novel biomaterials, such as collagen, chitosan, pullulan, hydroxyapatite, cellulose, gelatin, and carbon-based nanocomposites, can be derived from biowaste through bioprocessing. This paper demonstrates to what extent we have succeeded in transforming biowaste into biomaterials with commercial value. Furthermore, this article discusses the most recent developments in waste valorization and circular economy concepts and the promising future of transforming agro-industrial wastes into functional biomaterials and their applications.

1. Introduction

Waste management is a major concern in today's society. Population growth, industrial expansion, and widespread economic prosperity are just a few of the factors that have contributed to the accumulation of waste. The World Bank estimates annual waste output at 2.01 billion metric tons, with a potential increase to 3.40 billion metric tons by 2050 (Kaza et al., 2018). Most trash is burned, chemically treated, dumped into waterways, or buried in landfills. Forty percent of garbage is simply dumped with no further processing. Poor waste disposal is hazardous to people's health and the environment because it pollutes the air, water, and soil and facilitates disease transmission (Tyagi & Kumar, 2021). People are now considering how productive various waste materials can be due to new technologies and standards focusing on making energy from waste. However, there are a few drawbacks that reduce environmental sustainability and waste management efficiency. Agro-industrial waste, produced when agricultural items are processed industrially, accounts for a significant portion of global garbage. Liquid and solid waste streams from processing, such as peels, seeds, pomace, and byproduct streams, are high in biomass and contain a wide range of essential nutrients. These wastes could be used as low-cost and efficient raw materials to create value-added products, such as pigments, bioactive compounds, enzymes, and biofuels (Mishra et al., 2018, 2019).

Industrial biotechnology has enabled the development of new methods of reusing waste that are more cost-effective and long-lasting than older methods. Submerged and solid-state fermentation are biotransformation processes that convert agro-industrial byproducts into marketable goods. In addition to using waste and addressing environmental issues, wholesale production of augmented goods provides a strategy for boosting the green economy in pursuit of goals for long-term sustainability. Given the Earth's severe difficulties in resource use and waste generation, circular economies (CEs) have been proposed as a solution to shift away from linear systems and toward more cyclical ones. Despite their obvious advantages, fully circular systems are not always self-sustaining (Barros et al., 2021). The circular bioeconomy (CBE) concept was developed on the premise that shifting to a renewable-

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resource-based economy could reduce adverse environmental effects (Mishra et al., 2023).

Bioeconomy (BE) is driven by the manufacturing and transforming sustainable natural resources into high-value bio-based products, such as food, feed, medicines, biochemicals, and electricity (European Commission, 2018). The boldness of organic matter plays a vital role in generating food, fodder, and biofuels for transportation (de Souza & Pacca, 2021) and power, thermal energy, and the construction of structures (Barros et al., 2021). However, all businesses, including those in the BE sector, have had a difficult time in recent years due to the effects of the COVID-19 pandemic on the three pillars of sustainability (Ranjbari et al., 2021). Santagata et al. (2021) discovered a circular bioeconomy strategy for food waste and comprehensively examined the processes involved in recovery and recycling. The primary objectives that have been reported, include improved resource management, prevention of economic losses, the creation of employment opportunities, and the ability to influence stakeholder behavior.

This critical review investigates the current trends and feasibility of integrating biowaste into the circular bioeconomy, while highlighting the potential of bioconversion of agro-industry biowaste into biomaterials *via* microbial factories as a promising domain of the circular economy (Seng et al., 2021; Sze et al., 2020). Therefore, a CE theory is proposed to use renewable resources, emphasizing the importance of inherent wastefulness for environmentally responsible crop management. To better use the waste produced, the agricultural industry has adopted a circular economy to reduce waste production and increase waste value through economically viable methods. Furthermore, several valuable metabolites, energy, and materials may be created by processing agricultural waste, which might be commercialized to enhance bioproduct technologies. With an eye toward a secure future, this research details agricultural biomass production and bioeconomic perspectives.

This paper describes the progress in converting biowaste into biomaterials with marketable properties. The current study summarizes the current state of the art and the promising future of converting agro-industrial wastes into valuable biomaterials and their applications, focusing on waste valorization and the circular bioeconomy.

2. Most commonly available agro-industrial biowaste

Biomass is the main component of biowaste, and it decomposes in aerobic and anaerobic environments (Romero-Güiza et al., 2016). Good biowaste management is essential in protecting the environment and improving living conditions. Furthermore, when combined with value-addition, it has the potential to solve energy and waste management issues while also making money. Table 1 summarizes the benefits and drawbacks of using various biowastes for biomaterials, and the potential challenges.

2.1. Paper industry wastes

Pulp and paper are the third-biggest pollutants (Rahman et al., 2014). Pulping destroys the wood bonds. The paper industry employs chemical and mechanical methods to convert wood into pulp. The pulping process influences pulp quality and yield. The pulp for newspaper and tissue paper is produced mechanically. Sulfite pulping is used to produce specialty rayon, paper, and photographic film. Containerboard pulp is produced chemo-mechanically (Kamali & Khodaparast, 2015; Rahman et al., 2014). Pulping processes generate diterpenes, chlorinated resin acids, juvabione, and unsaturated fatty acids (Kamali & Khodaparast, 2015). Pulping, deinking, and wastewater treatment yield solid waste. For example, 1 ton of paper yields 40–50 kg of sludge (Kamali & Khodaparast, 2015). These organic-rich industrial wastes could harm marine and terrestrial ecosystems if dumped in the open environment. These wastes can be used immediately in anaerobic digestion and other waste-to-energy technologies (Rahman et al., 2014).

2.2. Food industry waste

Food processing units, restaurants, and grocery stores have proliferated to match population expansion. Progress in waste management has led to food waste accumulation (Ravindran &

Table 1
Opportunities and environmental problems of biowaste and its valorization to biomaterials.

Biowaste types	Opportunity to create value-added products	Major environmental concerns	Reference
Paper industry waste	• High organic content • Easily separable, homogeneous, and processed with minimal effort.	• Depending on the pulping method, several waste products may be created. • Open disposal can result in odors and contamination. • High sulfides, bases, and acids disrupt fermentation and necessitate specialized pretreatments.	Kamali & Khodaparast, 2015; Rahman et al., 2014
Food industry waste	• Easy to collect • It can assist in eradicating stench concerns and many health and environment issues. • Food waste like oils can be converted directly into biodiesel using	• Require pretreatment to convert complex polymeric material into free sugars. • Oil characteristics are impacted by increased operational temperatures and produce free fatty acids that affect biodiesel profitability. • Possibly excessive in salts, which would interfere with fermentation using microbes	Bernstad Saraiva Schott et al., 2016; Mishra et al., 2019, 2022; Ravindran & Jaiswal, 2016
Animal foods processing waste	• With its abundant organic material and microbial flora, bio waste can be utilized directly for anaerobic digestion to generate biogas. By trans esterifying cattle oils and fats with alcohol, biofuel can be made immediately	• Anaerobic digestion requires a large tank and processing vessel, from which Fumes could result. • Recovering fats and oil from leftover meat necessitates pre-processing steps.	Nagai et al., 2001; Nouri et al., 2016; Santagata et al., 2021
Municipal solid waste	• It can be directly used in anaerobic digestion processes. Greywater has an abundant supply of organic and nutrient - rich matter for algae development, which enhances waste management and quality of life.	• There is much odor, so it needs to be done in a special, sealed-off area.	Ebrahimian et al., 2020a; Lee et al., 2020; Stąsiek & Szkodo, 2020

Jaiswal, 2016). Breweries, meat processing plants, candy factories, and vegetable oil plants all produce large amounts of waste (Ravindran & Jaiswal, 2016). Non-standard fruits, fruit peels, pulp, and filter sludge are examples of solid wastes. Starch, sugar, and solid organic matter are the liquid wastes from washing fruits, vegetables, and meat. After a few uses, cooking oils are discarded. By 2020, the annual production of used cooking oil is expected to reach 18 million tons (da Silva César et al., 2017). Since it does not dissolve in water, it is dumped directly into the environment, which is extremely harmful to the environment. Biorefineries convert food waste into biofuels, enzymes, and nutraceuticals.

2.3. Animal food processing wastes

Dairy and poultry farms in third-world countries generate a lot of animal waste in the form of manure or meat processing byproducts. The animal wastes from meat treatment facilities consist of flesh, fur, tallow debris, meat, skeletons, and plumes (Bernstad Saraiva Schott et al., 2016). These include things with a lot of organic matter, which can make things smell and, if not treated, can lead to the growth of harmful microorganisms. This natural decomposition mechanism produces methane, a more harmful gas than CO_2. In addition, animal waste tank runoff can contaminate groundwater. As a result, animal waste conversion to biomaterials has gained momentum in the past few years (Santagata et al., 2021).

2.4. Municipal solid wastes

Population growth, urbanization, and economic development increase municipal solid waste (MSW). A resident of a developing or emerging nation produces 100–400 kg of MSW annually. Every ten years, MSW production doubles, reaching 2.2 billion tons by 2025 and 4.2 billion tons by 2050. Mistreatment of MSWs has been documented in Thailand, Bangladesh, India, and China (Ferronato & Torretta, 2019). Governments and waste management bodies in developing and growing countries are facing challenges. MSW is managed through landfills, recycling, and thermal and biological treatments. Waste-to-energy involves merging landfill and waste combustion technologies for energy recovery (Cheng & Hu, 2010; Lee et al., 2020).

3. Biowaste treatment valorization technologies

Because of the state of the economy and the environment, we must all do our part to recycle and reduce waste. Numerous conventional and innovative approaches, along with technologies, are persistently emerging and improving to enable the conversion of waste into valuable resources, such as fuels, biological chemicals, and materials. As a result, a wide range of approaches to modifying and transforming substances can be used, most of which can be classified under the headings of biology and chemistry (Lee et al., 2019).

3.1. Biological conversion technologies

Waste that has undergone a managed transformation by living organisms is said to have undergone a biological treatment process. These also include biochemical conversion processes (Lohri et al., 2017). In contrast to thermochemical transformations, biochemical reactions require far less energy input but move much slower. Traditional biological and chemical processes, such as anaerobic digestion, alcohol fermentation, and photobiological methods, can produce biofuels (Lee et al., 2019; Lohri et al., 2017).

3.1.1. Composting

Composting, or the controlled aerobic breakdown of organic materials, is centuries-old. Compost can be made from various organic solid wastes, including green waste (grass, branches, woodchips, and leaves), agricultural waste, food waste, manure, and even human feces (Lohri et al., 2017). Microbes come in various forms, and they all work together to decompose organic compounds into water, heat, and carbon dioxide. Therefore, it is vital to adjust organic material content, grain size, ventilation, warmth, hydration, and ionic strength to hasten decomposition and generate high-quality compost (Dedinec et al., 2015). In addition, given that this method depends on dynamic microbial activity, it is necessary to monitor the moisture levels of the feedstock and supplement them with water throughout the process (Taiwo et al., 2016). When done correctly, it goes through three stages: (1) the mesophilic phase, (2) the thermophilic phase, and (3) the cooling and maturation phase (Lohri et al., 2017).

3.1.2. Anaerobic digestion

Biomethanation or biomethanization is a robust method for decomposing liquid and solid organic matter by interfering with bacterial activity in an anoxic environment (Vögeli et al., 2014). Anaerobic digestion has expanded beyond its original context in wastewater treatment to include the organic fractionation of agricultural and municipal solid wastes (Jimenez et al., 2015). Industrial food waste (including slaughterhouse waste), sewage sludge, energy crops, and algal biomass are all materials that can be used as anaerobic digestion feedstocks (Romero-Güiza et al., 2016). Fermentation (acidogenesis and acetogenesis), hydrolysis, and methanogenesis are the steps involved in the anaerobic biodegradation of organic materials into CH_4, CO_2, and trace amounts of H_2S. Fermentation employs the simple biomolecules produced during hydrolysis to produce ethanol, acetic acid, volatile fatty acids, and H_2 and CO_2 gas mixtures. Biogas is generated when methanogens metabolize a gas mixture into mainly CH_4 (60%–70%) and carbon dioxide (CO_2) (30%–40%). Methanogenesis is stimulated by several factors, including the primary biomass nutrients (C, N, and P) and the trace elements (iron, zinc, and cobalt) (Lee et al., 2019). Lipid-based biomass hydrolyzes more slowly than carbohydrate- and protein-based biomass but produces more methane overall due to its higher lipid content. Many factors influence biogas yield and energy content, including the nutrient profile of the biomass, temperature, pH, and the rate at which the biomass is loaded. Methanogenesis depends on an ideal operating pH for the formation of CH_4 in biogas. The energy content of biogas increases as its pH increases (due to a gradual increase in NH_3 concentration), as CO_2 is dissolved in the fermentation broth, and as CH_4 concentration increases. An acidic environment and a high working temperature stimulate microbial activity and CH_4 generation (Günerken et al., 2015).

3.1.3. Alcoholic fermentation

Yeast or bacteria are used in the alcoholic fermentation of biomass containing fermentable sugars transformed from the cellulose and hemicellulose of biomass into bioethanol. Microalgae like *Scenedesmus*, *Chlorella*, *Spirulina*, and *Dunaliella* has been discovered to store substantial quantities of glycogen, cellulose, and starch (Lee et al., 2019). These complex polysaccharides can be used as feedstock for bioethanol synthesis. As bacteria have trouble metabolizing polysaccharides, hydrolysis is done before feeding to convert polysaccharides into monosaccharides. Sugars can be hydrolyzed with acids, bases, or enzymes, with the former being the most prevalent. Although sugars can be quickly and easily converted in acidic environments, the benefits of these quick and inexpensive therapies are not without drawbacks. Enzymatic

processes are efficient and waste-free, but they are costly and complex (Lee et al., 2019). Hydrolysis efficacy and time can be increased by performing primary cell disruption operations (Günerken et al., 2015). For the raw alcohol (10%−15% ethanol) produced, ethanol concentration *via* distillation is required (Bibi et al., 2017). Thermochemical processes (liquefaction, gasification, or pyrolysis) convert the residual solid waste into valuable byproducts. Scientists are currently investigating the prospect of modifying the DNA of specific microalgal strains to increase their production of lucrative byproducts. One such initiative is based on using photosynthesis to convert CO_2 directly into biofuels via genetic modifications. Along this pathway, no additional energy is needed to synthesize or break down the proteins necessary for storing energy and cellular structure. Plants use the Calvin cycle to generate glucose and other metabolites, in which ribulose-1, 5-bisphosphate, combines with carbon dioxide to form two 3-phosphoglycerates (John et al., 2011). Instead, researchers have been working on implanting genes necessary for ethanol production into cells that produce 3-phosphoglycerate, rerouting the molecule to construct ethanol.

3.1.4. Photobiological hydrogen production

Microalgae have the intrinsic ability to generate hydrogen gas when exposed to light. An enzyme called hydrogenase lowers H^+ to H_2 without oxygen during photosynthesis. As a result, the process emits O_2 gas, which inhibits the hydrogenase enzyme and prevents H_2 gas formation. Consequently, microalgae grown for H_2 generation require anaerobic conditions (Lee et al., 2019). The photosynthetic H_2 of microalgae can be harvested in two ways. First, when light is present, we can take advantage of the simultaneous production of O_2 and H_2 gas, and the two gases can react. Second, hydrogenase enzymes utilize the electrons released during the oxidation of water molecules to generate hydrogen gas. The second strategy employs a two-stage method: the first cultivates the microalgae under standard conditions, and the second promotes continuous H_2 production in anaerobic and low-sulfur settings. Theoretically, technique one produces more hydrogen gas than technique two, but O_2 quickly stifles H_2 production (Lee et al., 2019). By temporarily activating the PSII system without an aerobic environment, H_2 generation in low-sulfur cultures is perpetuated for extended durations. With a periodic injection of sulfur, cell reconstitution and a threefold increase in total H_2 yield were achieved compared to control cultures with no added sulfur (Kim et al., 2010).

3.1.5. Transesterification (acid/base and enzyme catalysis)

Biodiesel production via transesterification employs three catalysts: acids, bases, and enzymes. In contrast to acid-catalyzed transesterification, base-catalyzed transesterification can produce substantial yields of fatty acid methyl ester quickly and with highly mild reaction conditions, making it a standard industrial process. While enzymatic catalysts are environmentally friendly and produce high-quality results, they still require refinement before being employed in commercial settings. To make biodiesel, a two-step esterification and transesterification method is usually employed. The granular lipid content can be converted into biodiesel utilized in conventional internal combustion engines by *trans*-esterifying triacylglycerols to generate fatty acid alkyl esters (catalyst being acid, base, or lipase). Due to the high energy consumption, significant water and salt demands, and demands on conventional transesterification processes, the development of enzymatic esterification reactions mediated by intra- or extracellular lipases was pursued (El Muller et al., 2014). However, because of their sensitivity to alcohol and heat, enzymes as catalysts often produce lower biodiesel yields than other options. Protein engineering, immobilized enzymes, and whole-cell catalysts are only a few approaches for increasing the efficiency of enzyme catalysis. Nano-MgO, nano-SiO_2, and nano-ZnO (heterogenous catalysts) converted *Mangifera indica* oil into biodiesel. Nano-SiO_2 significantly affected catalytic reactivity and drove reactions to obtain maximal yields because of its highly acidic characteristics (Jadhav & Tandale, 2018). This demonstrates that heterogeneous catalysts are effective in converting feedstocks into biodiesel, which has the added benefit of being recyclable (Sharma et al., 2018). The traditional two-step esterification procedure for making biodiesel from *Pongamia pinnata* crude oil is unnecessary. The same results can be obtained with a one-step direct transesterification process using sequential acid-base catalysis. This procedure was replicated using transesterification-transesterification techniques (Yunus Khan et al., 2018). The 1.5-fold reduction in production time required for biodiesel products is one of the most encouraging aspects of direct transesterification technology.

3.2. Thermochemical conversion of biowaste

At very high temperatures, organic compounds are broken down and reformed into biochar (a solid), syngas (a gas), and oxygen-enriched bio-oil (a liquid) (Lee et al., 2019). Thermochemical conversion typically involves one of three methods: gasification, pyrolysis, or liquefaction. The decision-making process is influenced by biomass feedstock type and quantity, energy output, and environmental considerations (Chen et al., 2015). However, many studies have shown that thermal conversion technology is the best choice for the industry. It employs cutting-edge thermochemical conversion technology, works faster, uses less water, and can convert waste plastics into energy (Uzoejinwa et al., 2018). It has been recognized as a simple and efficient method of producing value-added biofuels.

3.2.1. Torrefaction

Torrefaction is a mild thermochemical process typically occurring between 200 °C and 300 °C in an airless environment (Shankar Tumuluru et al., 2011). The degradation reactions weaken the fibrous nature of the biomass and increase its carbon content while maintaining a high solid yield (Sarker et al., 2021). Water vapor, smoke, oxygen, and hydrogen are reduced during combustion. When the oxygen-hydrogen ratio decreases, the carbon-hydrogen ratio rises, and thus the calorific value of biomass rises (Patra et al., 2022). The product's high hydrophobicity increases friability (Robbins et al., 2012). Biochar does not decompose or attract microorganisms; hence, it can be stored indefinitely without risk of spoilage. The resulting biomass is sold on the open market as a smokeless, solid fuel and is also utilized in power plants as a co-combustion agent alongside coal (Kundu et al., 2018).

3.2.2. Pyrolysis

The pyrolysis process involves the thermal decomposition of organic waste in anoxic conditions at temperatures ranging from 350 °C to 550 °C and can even exceed 700 °C. Pyrolysis oil (py-oil) or bio-oil, a liquefied fuel produced during the pyrolysis process, can replace fuel oil for heating applications or electricity generation. Producing bio-oil from pyrolysis has the advantage of being a liquid, making it more convenient for storage and transport than the fuel gases created by the gasification process (Dhyani & Bhaskar, 2018). Slow, rapid, and flash pyrolysis are the three main categories of pyrolysis processes, distinguished by their respective temperatures and pressures. Slow pyrolysis at low temperatures, higher heating rates, and a long vapor residence time contribute to biochar production. Contrarily, fast pyrolysis, in which temperatures are kept at or below 500 °C and residence periods are kept to a minimum, mainly yields bio-oil.

Flash pyrolysis, in contrast, has a much shorter reaction time and heating rate than rapid pyrolysis. Flash pyrolysis is being thoroughly investigated to create liquid fuel because of the substantial py-oil yields of over 75 wt% and the advantages of minimally charged, energy-efficient, and environmentally benign technology (Lee et al., 2019). Further, work is being done to enhance py-oil quality as a drop-in replacement for regular oil. The physical upgrading of bio-oil by hot vapor filtration reduces its primary particle size, which delays the breaking down of oil over time (Rahman et al., 2018).

3.2.3. Gasification

Biomass gasification, or syngas synthesis, is an oxidation process at high temperatures (Reddy et al., 2016). The byproduct gas is a mixture of several components, including but not limited to CH_4, CO, H_2, and CO_2. Like other thermochemical conversion processes, gasification generates biochar, bio-oil, and combustible syngas. Like other thermochemical conversion processes, gasification generates biochar, bio-oil, and combustible syngas. Syngas can be converted into hydrogen gas, biofuel, biomethane, heat, electricity, and chemicals, among other forms of energy and fuel. Compared to pyrolysis and torrefaction, gasification can be performed in the air at temperatures between 800 °C and 1200 °C. Gasification is one of the most effective methods for extracting hydrogen gas from biomass (Ahmad et al., 2016). The efficient utilization of biomass feedstocks for heat and electricity generation means that biomass gasification can recover more energy than combustion or pyrolysis. As a result, biowaste gasification is widely regarded as the most effective method of recycling a wide variety of biomass feedstocks, including those from the food and beverage industries and household and industrial waste streams. Gasifying agents like oxygen and steam are used in the gasification process, and several variables influence the outcome of the process. These variables include gasifier type, gasifying agent, catalyst, particle size, equivalency ratio, temperature, catalyst, feedstock, and reactor type (Robbins et al., 2012). In retrospect, the gasification process generates massive amounts of CO_2 and CO from source materials rich in carbon and oxygen, such as municipal and agricultural waste (Watson et al., 2018).

Furthermore, releasing sulfur as H_2S complicates gas separation and treatment, necessitating gas treatment techniques for feedstock with high sulfur content. According to a study by Salimi et al. (2018) on energy production from lignocellulosic waste, hydrothermal gasification techniques utilize new alloyed precursors built on activated graphene and carbon nanosheets. Metal-based catalysts accelerating the reforming reaction can increase hydrogen and methane generation (Salimi et al., 2018). By heating and maintaining high temperatures with external energy, plasma gasification can convert potentially dangerous organic matter, primarily into syngas and ash. Bandages, biological waste (cytotoxic medicines, antibiotics), and laboratory trash containing biomolecules or organisms are all medically related products that can be treated by the plasma gasification method (Messerle et al., 2018).

3.2.4. Liquefaction

Liquefaction processes generate bio-oils at low temperatures and high pressures, with or without catalysts and hydrogen. Hydrothermal liquefaction (HTL) is a proven method for converting biomass into bio-oil by employing subcritical water at temperatures between 250 °C and 374 °C and pressures between 40 and 220 bars. Chemicals dissolved in water, solid sediments, and gases and the decomposition and repolymerization reactions involved in bio-oil conversion are all components of HTL processes (Dimitriadis & Bezergianni, 2017). High-moisture-content biomass is commonly used in the HTL process because it reduces the need for a drying or dewatering step, resulting in cost savings. As a result, biomass feedstocks with appropriate moisture content, such as algae and woody biomass, are ideal for bio-oil synthesis. Due to its composition, which consists primarily of hemicellulose (15%–35%), lignin (20%–35%), and cellulose (30%–50%), woody biomass is an appropriate feedstock for HTL. Both the presence of a catalyst and the solvent used affect the amount of bio-oil extracted from woody biomass. Since deep eutectic solvents are advantageous in many ways, including being simple to produce, non-toxic, and stable at low temperatures, Alhassan employed them as a stimulant in the hydrothermal transformation (HTL) of deoiled Jatropha cake. Approximately 41%–54% of the high-energy bio-crude was reportedly recovered in the study (Alhassan et al., 2016). Another study led by Costanzo et al. investigated the extraction of bio-crude oil from algae. They employed a two-step HTL process, first employing a low-temperature HTL and then a high-temperature HTL in conjunction with hydrodenitrogenation and hydrodeoxygenation catalysts. The resulting crude was comparable to conventional gasoline (Costanzo et al., 2016).

3.3. Advanced and hybrid conversion technologies

3.3.1. Advanced HiTAG/HiTSG technology for efficient conversion of biomass and municipal waste

An innovative new method called high-temperature airflow and air/steam (HiTAG/HiTSG) thermochemical transformation of solid waste from municipalities into biofuels, such as hydrogen, syngas, and electricity, has the potential to have significant environmental advantages (Stsiek et al., 2020). Many scientific institutions have active research and development programs to maximize the use of various types of biomass and municipal waste (Oumer et al., 2018). High-temperature conversion technologies can achieve more than 90% conversion efficiencies and manage a wide range of biomass and waste streams. Drying, pyrolysis, gasification, and combustion are the main physicochemical processes used in heat conversion (Fasolini et al., 2019). Gasification is a more effective and cleaner alternative to direct incineration for converting biomass and MSW to fuel. In contrast, if cutting-edge, low-cost ideas like HiTAG were developed, they could aid in mitigating environmental damage. This processing facility includes a ceramic regenerator to heat the feed gas to the proper temperature, a steam generator, an H_2 separation ceramic membrane, and a gas cleaning machine, among other components. A small preheater provides a high-temperature (up to 1600 °C) air or air-steam mixture to aid the transformation. Almost any dry organic matter can be gasified to produce a clean-burning fuel at high temperatures and pressures (HiTAG/HiTSG) (Li et al., 2019). This cutting-edge method could replace fossil fuels in most applications and reduce greenhouse gas emissions (Stsiek et al., 2020). It aims to achieve high-level thermal conversion of biomass and waste to fuel gas under various situations.

3.3.2. Hybrid thermo-biochemical process for adept lignocellulosic biomass conversion

Traditionally, lignocellulosic biomass was processed either biochemically, by converting biomass into reduced sugars through pre-treatment and microbial fermentation to yield fuel products, or thermochemically, by pyrolysis or gasification to yield intermediate products such as syngas or bio-oil for use in the production of fuels and chemicals (subjective to upgradation). Another option is hybrid treatments, such as a sequential thermochemical–biochemical approach (Shen et al., 2015). Depending on the thermochemical process mode chosen, the blended thermochemical–biochemical process may begin with accelerated biomass pyrolysis to pyrolytic substrates or with microbial fermentation of feedstock to syngas. Hybrid methods pave the way to advanced biofuels that perform

similarly to petroleum-based transportation blends. Hybrid methods combine the best features of traditional thermochemical and biochemical approaches while minimizing their drawbacks. Since thermochemical methods can overcome biomass resistance, there is no need for time-consuming and costly pre-treatment procedures or enzyme combinations. It can convert any biomass into fermentable intermediates, independent of its composition (Daniell et al., 2012). In addition, microbial fermentation can be easily scaled up since it can be done effectively in ambient conditions. Fast pyrolysis is a phase in the pyrolysis-fermentation process that yields primitive bio-oil and can be done close to the biomass production facility. Furthermore, unwanted oxygenates, such as polysaccharides and organic acids, can be subjected to microbial fermentation to generate fuels and chemicals, and undefined biofuels can be transformed into drop-in hydrocarbon fuels (Bridgwater, 2012).

3.3.3. *Integrative treatment process for solid organic waste*

MSW, which includes food scraps, yard trimmings, and sewage sludge, is produced in massive quantities by large urban areas worldwide. Rising energy demand and a lack of landfill space are major global challenges (Bernstad Saraiva Schott et al., 2016). Incineration can lessen MSW output but also generate much ash that must be managed. Anaerobic digestion, a low-cost method for treating organic waste and recovering bioenergy, can also be used under anoxic conditions to convert organic matter into biogas (20%–40% CO_2 and 50%–70% CH_4) (Garfí et al., 2016). However, anaerobic digestion (AD) can only treat organic waste broken down by microorganisms, like food scraps, animal manure, and sewage sludge.

Furthermore, natural breakdown by AD is not economically practical because refractory materials like wood contain high levels of lignin, cellulose, and hemicellulose that must be removed through costly pre-treatments (Romero-Güiza et al., 2016). For the most part, carbonaceous solid wastes can be treated, and thermal energy can be generated through thermal processes, such as gasification. In contrast to incineration, which only recovers thermal energy, gasification can convert all types of carbon-containing solid waste into marketable gases (CO, CO_2, H_2, and CH_4) and other significant commodities (Watson et al., 2018). Therefore, the development of a hybrid system is required to process various MSW types and efficiently recover energy. Fig. 1 outlines the various sources of biowaste and their valorization techniques across biowaste and technology boundaries.

AD and gasification make it easier to convert trash into energy using a distributed energy system. A decentralized waste-to-energy system can manage multiple types of solid wastes that are energy-efficient and inexpensive to transport. Waste treatment solutions such as dispersed anoxic gasification/digestion stations and monolithic incineration plants present a promising and appealing approach to better waste management (Zhang et al., 2018). Researchers developed a system that converts waste into biological and thermal energy using a gasifier and a distributed AD reactor. The decentralization potential and size of waste facilities in a hybrid conversion system vary depending on resource availability, spatial constraints, and urban planning. A pilot study used a 1000 L AD reactor to convert biodegradable food waste into biogas. A 10 kW gasifier was used to process the dry solid waste, and producer gas was obtained from wood chips. Biogas was mixed with product gas and used in other applications that required more heat. During gasification, the waste heat was used to warm the mesophilic AD, creating an internal heat recovery mechanism that made biodegradation possible (Zhang et al., 2018). However, unified waste-to-energy schemes have yet to be studied to determine how underlying heat recovery systems affect energy usage efficiency.

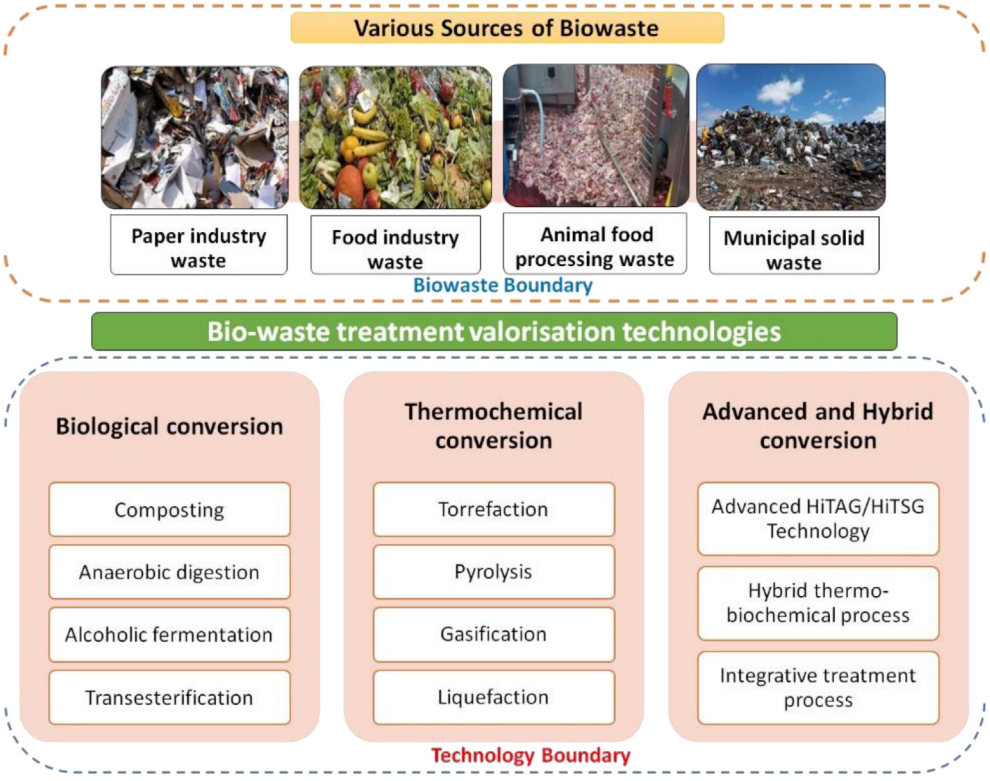

Fig. 1. Outline of potential origins of biowastes and available methods of valorization to obtain value-added products.

4. Biowaste to biomaterials

Biomaterials are developed to fabricate biomedical devices that perform the same or similar functions as the human body. For direct contact with living organisms, biomaterials must meet stringent requirements. These include functionalization, therapeutic acceptability (nontoxicity, non-allergenicity, non-hypersensitivity), tensile stability, optimum volume and compactness, and cost-effectiveness. The generation of such chemicals, whether from organic materials or recyclable scraps, is a significant problem under investigation in various ways. This section describes the production of various biowaste-based products. Fig. 2 illustrates the conversion of different groups of biowastes into specific functional biomaterials.

4.1. Collagen and collagen-based biopolymers

Collagen can be recovered from a variety of meat processing wastes, most notably pig flesh (46%), bovine hides (29%), and swine and cattle bones (23%), which account for 30% of mammal protein content. Collagen contains glycine at a 33% concentration and a high proportion of proline and hydroxyproline residues (23% of the total amino acid composition). Making gelatin involves heating collagen until it becomes gelatinous. It is inexpensive and widely available. Casting, extrusion, and electrospinning are just some of the methods developed to use this material's biodegradability, pliability, and moisture/oxygen barrier qualities, all of which make it ideal for use in food and medical applications (Gómez-Guillén et al., 2011).

Collagen types I, II, and IV have been successfully isolated from animal skin, bone, scale, and cartilage using an environmentally friendly method that also adheres to the European Union's zero-waste goal. Combining mechanical processes, including pH modification, homogenization, and sonication, with acids, saline, and enzymatic processes, allows collagen to be successfully recovered and processed from fish, echinoderms, and jellyfish waste. Many marine animals, particularly dinoflagellates, cephalopods, starfish, jellyfish, and various fish, have had collagen type I isolated from their tissues. The qualities of marine collagen include excellent film-forming ability, cytocompatibility, minimal allergenicity, significant environmental friendliness, and cell growth potential. These qualities are useful in nutraceuticals, cosmetics, and biomedicine as drug delivery vehicles or wound dressings. Collagen is desirable for texturizing, coarsening, and gel production due to its high-water absorption capacity (Gómez-Guillén et al., 2011).

Keratin, collagen, elastin, and fibrin are all fibrillar proteins found in living creatures. For example, fibrinogen (fibrin precursor protein)-rich blood can account for 4%–7.5% of an animal's total weight. In comparison, the protein content of blood varies by species but rarely exceeds 30% (Kerton et al., 2013). Collagen is the most abundant protein in mammals, accounting for more than 30% of total protein content.

Collagens utilized in the commercial sector are extracted using enzymes from animal muscle tissue, which employs acid, essential, or balanced solubilization techniques. However, these procedures are costly because of the low to medium extraction yields and the collagen degradation during the process. For instance, enzymes may split the cross-linked terminal region of collagen, producing feeble mimics of healthy cells. As a result, biowastes, specifically the organic portion of fish waste have been investigated as a cheap and environmentally friendly source of collagen in the search for ways to increase outputs and formulations (Gómez-Guillén et al., 2011; Katarzyna et al., 2020; Shenoy et al., 2022).

4.2. Chitin and chitosan-derived biomaterials

The aquaculture industry generates much biowaste, which might be used as a source of raw materials to make things like chitin and chitosan, which have commercial uses. Multiple studies have demonstrated the efficacy of bacterial proteases in deproteinization—enzymatic deproteinization of mineralized shrimp waste results in chitin and a protein hydrolysate rich in nutrients.

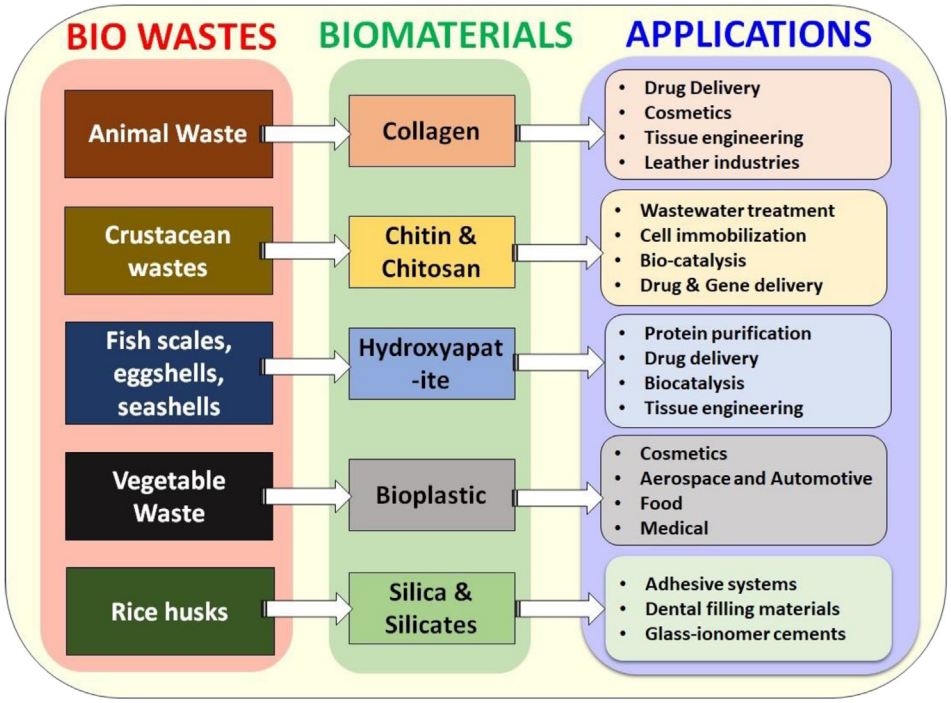

Fig. 2. Systematic look at how biowaste is turned into biomaterials and what it can be used for.

Chitosan is theoretically created annually, mainly from leftover shrimp, fish scales, and crab shells. With rising fisheries, aquaculture, and seafood consumption comes a corresponding rise in biowaste that can be recovered economically as competent polymers (Oliveira Cavalheiro et al., 2007). A crustacean shell comprises about 20% calcium and magnesium carbonate, 20% protein, and 15% chitin (Kerton et al., 2013). Chitin and its primary metabolite, chitosan, are examples of natural amino polysaccharide polymers with biomaterial potential. Chitin from crustacean debris contains N_2, contrary to many other biomass types, and is frequently used in the pharmaceutical, CO_2 capture, or fabric industries to emulsify food ingredients. It is advertised as a supplement that reduces inflammation, promotes weight loss, lowers cholesterol, and balances blood pressure. Biodegradable polymers can be produced from chitosan. Chitin is found in 13.5%–43.8% of shrimp shell waste (Karnaouri et al., 2019) and 4%–37% of squid shell waste. It is estimated that between 16% and 20% of chitin from crabs and lobsters can be saved (Gogoi & Hazarika, 2017).

Commercial chitin is derived from crustacean byproducts of the fishing industry. The most frequent contributors are krill, lobster, prawns, crabs, and shrimp carapaces. Chitin makes up 20%–30% of the bulk of these biomass residues, protein 30%–40%, mineral salts, particularly calcium carbonate and phosphate, 30%–50%, and lipids 0%–12%. Since chitin is frequently found in crab shells, it must be isolated by removing protein, inorganic components, and coloring agents (canthaxanthin, astatine, astaxanthin, lutein, and b-carotene). At the same time, deproteinization (the removal of proteins) is carried out at room temperature through the solvent extraction process. Crystalline chitin stands out from other biomaterials due to its numerous advantageous properties, including biocompatibility, biodegradability, antimicrobial activities, antigenicity, and eco-safety. As a result, many chitin equivalents have been synthesized, including N- and O-sulfonated chitin (useful because of its resemblance to the blood anticoagulant heparin) and dibutyryl- and carboxymethylchitin (with biological uses in the delivery of drugs) (Peniche et al., 2008).

A different, similarly effective method of producing chitosan from shrimp shells involved the conventional processes of deproteinization and demineralization, accompanied by delignification (discoloration) using ethanol. After that, a NaOH (12.5 M) aqueous solution was added to the chitin, and the mixture was cooled and frozen for 24 h. The produced chitosan exhibited satisfactory physicochemical properties, including low ash content (0.063%), good solubility in acetic acid (1%), and a crystallinity index of around 40% (de Queiroz Antonino et al., 2017).

4.3. Hydroxyapatite

Hydroxyapatite ($Ca_{10}(PO_4)_6(OH)_2$) is one of many essential materials used as skeletal reinforcement materials and scaffoldings for implantable devices due to its bioactive components, bioactivity, and non-inflammatory nature. Natural wastes, like animal carcasses, eggshells, seashells, fish scales, and algae, have been suggested as potential starting points for hydroxyapatite extraction (Khoo et al., 2015). Bones from bovine, swine or fish species are often treated by washing them in an alkaline solution and then calcining them at temperatures between 600 °C and 1400 °C to remove any remaining proteins. Natural hydroxyapatite was isolated from bovine bones using three protocols: thermal breakdown, subcritical water, and alkaline hydrothermal processes (Khoo et al., 2015).

Polluting landfills with discarded eggshells is a common occurrence. Eggshell disposal costs approximately $100,000 annually in US egg processing facilities (Laca et al., 2017). Recycling this trash has both financial and environmental benefits. However, more research is needed to investigate recycling eggshells' commercialization and industrial upscaling potential. Depending on the heat used, trash can replace limestone ($CaCO_3$) or lime (CaO). The average price per ton for commercially ground limestone or lime is around $100. In addition, the intensity of the heat treatment results in differently colored material, which can affect the use of the scrap (Zahouily et al., 2005). Previous research has demonstrated the benefits of using eggshell ash instead of lime for treating soil (TAHIR et al., 2006). According to a life cycle assessment, the calcination process, which entails warming the mussel shells to 800 °C, has high energy expenditure. The conventional processing and production method for lime from limestone includes a heat treatment with the corresponding energy expenses. The $CaCO_3$ in eggshells has been used as a neutralizing agent in laboratory-scale demonstrations of eggshell waste valorization to synthesize fumaric acid (Adams et al., 2022). Eggshell waste has also been repurposed in the lab as an adsorbent for cleaning wastewater and drinking water. Recycling eggshells into high-value goods like hydroxyapatite can have a significant financial impact in addition to having a positive environmental impact. The cosmetics industry and a sizable industrial co-composting market have described small-scale pilot applications of eggshell waste commoditization. Since the organic substance on eggshells decomposes quickly, the optimal locations for eggshell retrieval are similar to those of processors.

The eggshell membranes and $CaCO_3$ shell are recycled, and eggshell waste is handled and processed by an egg processing company in the UK. The savings cover the cost of processing by avoiding landfill disposal. The business offers inexpensive $CaCO_3$ powder from eggshells as plastic fillers. While the polymer costs over $2000 per ton, conventional limestone $CaCO_3$ powder costs only around $2000 per ton. Therefore, for eggshell $CaCO_3$ filler to have a more significant market role, its price must meet this requirement.

Another advantage of shelled $CaCO_3$ dust is its smaller particle size compared to ordinary limestone powder. Fine-tuning procedures like thermal processing, chemical modification, and physical treatment help lower processing costs. Price, availability, supply continuity, performance, and the need for conventional alternatives influence the industry's decision to use eggshell $CaCO_3$ powder.

4.4. Bioplastics

Bioplastics are organic polymers derived from feedstock and naturally degradable plastics that break down into organic compounds and hydrocarbons, primarily carbon dioxide when exposed to naturally occurring microbes such as fungi, bacteria, and algae. However, not all organic polymers are compostable because, unlike cellulose, cellulose acetate does not degrade in the ecosystem. Despite containing about 30% renewable carbon, bio-PET (polyethylene terephthalate) is not a biodegradable polymer like bio-based ethylene glycol. According to European Bioplastics, the primary forces driving this growth are fully bio-based and biodegradable biopolymers such as PHAs (polyhydroxyalkanoates) and PLA (polylactic acid), which are increasing global capacity for bioplastics production from roughly 2.05 million tons in 2017 to nearly 2.44 million tons in 2022 (Xu et al., 2019). Bio-PE (polyethylene) and bio-PET (polyethylene terephthalate), two nonbiodegradable polymers derived from biomass, account for more than 56% (1.2 million tons) of global bioplastics productivity. Bio-PE production is expected to increase due to the emergence of innovative complete bio-stationed alternatives such as bio-PEF (polyethylene furanoate), which has improved barrier and rheological properties for packaging beverages, fodder, and other products.

Bio-established PET production, in contrast, is expected to remain flat in the coming years. A new study has proposed using myofibrillar proteins derived from extracting the waste of gilded catfish (*Brachyplatystoma rousseauxii*) to create novel plastic materials. Following extraction, the proteins were mixed with aqueous glycerol (a plasticizer) and cast onto silicone supports, where they dried to form biofilms. The process design was optimized using response surface methodology to yield a bioplastic with 40% plasticizer (m/m) and 0.79% protein (m/v). The material is flexible, resistant, low in solubility, and permeable to water vapor due to its protein composition, making it ideal for food packaging.

Robust biofilms, with tensile strengths of 4.91 MPa, have been linked to sulfhydryl groups on the surface of myofibrillar proteins. Covalent S—S bonds could be made with these compounds. However, because fish muscle proteins are hydrophilic, the bioplastic was ineffective at keeping moisture out (water vapor permeability, WVP, was between 6 and 14 gm^{-1} s^{-1} Pa^{-1}). After all, they have polar amino acids and hydroxyl (OH) groups (Perotto et al., 2018). The mechanical properties of biofilms depended greatly on the type of biowaste from which they were made. For example, the residual silica in rice hulls stiffened the material, while the high concentration of triglycerides in cocoa pod husks caused the film to break under high stress and strain. These interactions, as well as the comparison of other characteristics (elastic modulus and how it interacts with water) with those of prevalent polymeric materials (polypropylene, polyethylene, and polyester) and kitchen waste, suggest that specific applications of biodegradable plastics in encasing and biomedical applications may be possible (Batista et al., 2019).

Another area of investigation in this research is the creation of recyclable plasticizers from organic wastes that can decrease the fragility, crystalline nature, melting point, and thermal properties of bioplastics while increasing their flexibility and toughness (Batista et al., 2019).

Plasticizers like poly(3-hydroxybutyric acid) and poly(lactic acid) are two examples of totally renewable materials (PHBs). Tannic acid (1,2,3,4,6-penta-O-{3,4-dihydroxy-5-[(3,4,5-trihydroxybenzoyl)oxy]benzoyl}-D-glucopyranose) is obtained from leftover lignocellulosic biomass. Citric acid, ethyl citrate (1,2,3-propanetricarboxylic acid, 2-hydroxy-, 2-ethyl ester), and bioethanol recovered from orange waste. It is also worth noting that synthetic plastics use more bio-plasticizers to replace conventional ones. Recently, it has been proposed that PVC, one of the most valuable polymeric materials, can be efficiently plasticized using highly divided polycaprolactone produced by solvent-free copolymerization of e-caprolactone and glycidol (a glycerol derivative), to name a few examples. Proponents claim that using these bio-based plasticizers instead of traditional petro-based chemicals like phthalate esters increases PVC's thermal stability and stretchability by a factor of 20 (Perotto et al., 2018; Xu et al., 2019).

4.5. Silica and silicates

Preparing silica and silicate salts from biowaste is becoming more popular. Plants initiate the dynamical circuit of silicon in the chemosphere by absorbing silicic acid (H_4SiO_4) from soil moisture. The hydrated amorphous silica then forms and accumulates in phytoliths, which gives plants their rigidity when the silicic acid polymerizes. Many aquatic and terrestrial plants have hydrated amorphous silica in their roots, trunks, foliage, husks, blades, and cores. Regarding biowaste, rice husks (RHs) represent one of the most silica-rich sources (20—22 wt% of rice grains). The applicability of bio-silica and its byproducts is becoming more appealing due to the silica concentration of calcium carbonate. Typical methods for extracting biogenic silica from RHs include acidic pretreatments to remove trace amounts of metals, followed by pyrolytic operations at temperatures and times ranging from 500 to 700 °C and 8—24 h, respectively (Adam et al., 2012; Xu et al., 2019). Another study suggested using rice husk, sugarcane bagasse, and bamboo culm—all renewable but inexpensive agricultural byproducts to remove SiO_2 *via* microwave-assisted solid-state ashing. The same study used MW-mediated magnesiothermic reduction to turn biogenic amorphous silica into pure crystalline Si. Unlike commercial Si nanopowders, the product had an easy-to-understand 3D porous structure. The pores were 50—80 nm in diameter, with walls 23 nm thick. Biowaste can be used to produce biogenic silicates by chemically extracting Ca from RHs or by using inorganic biowastes, such as egg or oyster shells, as a source of Ca to produce the necessary silicate salts (Shen, 2017; Shukla et al., 2022; Xu et al., 2019). A summary of reported biomaterials synthesized from various biowastes and critical findings have been enlisted in Table 2.

4.6. C-based and hybrid C-based nanomaterials

4.6.1. Carbon dots

Carbon dots are typically made using top-down approaches like laser ablation, arc discharge, and electrochemical reactions. However, bottom-up approaches, including hydrothermal, thermal, and microwave-aided processes, enable the construction of carbon dots from molecular predecessors. Carbon dots' carbonization, size, and shape can be tailored to a specific application due to their synthesizability; however, challenges in reproducibility between batches, surface property control, purification, and characterization may limit their practical use. The application of organic ingredients, notably biomass residues, has been investigated as preliminary substituents for manufacturing carbon dots, which can be made from various materials. Much new ground is ahead, and some new ideas are beginning to emerge. Some biowastes, such as fruit waste, fish bones, and RHs, react well to hydrothermally aided processing. According to a study, heating aqueous dispersions of citrus maxima peel for 3 h at 200 °C results in a stable carbon dot dispersion between 2 and 4 nm, an excitation peak at 365 nm, an emission peak at 444 nm, and a bright blue coloration under UV light (6.9% quantum yield).

Even without any label, these carbon dots worked well as sensitive tags, recognizing mercuric ions in the aqueous phase with a concentration range of 0.23 nm (Ashokkumar et al., 2012). A similar technique, starting with orange seed coat debris, produced carbon dots with an average particle diameter of 2.9 nm and a PL quantum efficiency of 2.88%. Potential uses in nanobiotechnology were posited due to the restricted size distribution. A microwave-assisted hydrothermal approach has also been used to produce carbon dots from biowaste, focusing on processing an aqueous environment of geese plumage, a significant poultry industry waste, at 180 °C in a microwave autoclave (2 kW). A solution containing carbon dots (Mw = 3500) was dialyzed against Milli-Q water to produce a homogeneous dispersion of them (Ashokkumar et al., 2016).

4.6.2. Nano-carbons and nanocomposites

As useable synthetic pathways beginning with biowastes have been implemented, there has been a recent uptick in interest in nano-carbon collagen, primarily made from leather waste, which shows promise as a potential source. In one of the early waste-to-wealth techniques, collagen was recovered from goat flesh cutting. The recovered collagen was treated by ignition at temperatures ranging from 500 °C to 1000 °C in an argon flow (Ashokkumar et al., 2016; Lakshmi et al., 2018). Onion-shaped C-based nanostructures up to 20 nm were created; each was

Table 2
Comprehensive summary of reported biomaterials synthesized from various biowaste.

S.L No	Name of biowaste	Prepared biomaterials	Key findings	Reference
1	The skin of marine puffer fish	Collagens	• Acid-soluble collagen (ASC) 43.1% and Pepsin-soluble collagen (PSC) 56.6% were made. • NIH_3T_3 cell lines showed that both types of collagen were 100% biocompatible.	Iswariya et al. (2018)
2	The outer skin of cuttlefish (*Sepia lycidas*)	Collagens	• A solubilized collagen (PSC) was made with 10% pepsin (w/v) and a 35% yield (dry weight basis)	Nagai et al. (2001)
3	Fish bones	Hydroxyapatite powder	• The powder's particles ranged from 0.657 to 19.81 m, with a mean size of 3.259 m.	Abdulkadhim and Abdulameer (2021)
4	Skin of brown-backed toadfish (*Lagocephalus loveri*), processing wastes	Collagen	• Compared to other vertebrates, the total amount of collagen that could be extracted was 54.3% based on lyophilized dry weight.	Senaratne et al. (2006)
5	The skin of *Brama australis*, the fish from the warm-water sea	Collagen	• The skin of *B. australis* produced about 1.5% collagen based on the wet weight of the raw material.	Sionkowska et al. (2015)
6	Egg shell	Flower-like Hydroxyapatite nanostructure	• The Hydroxyapatite nanostructure was a good substance with biocompatibility, drug adsorption/desorption behavior, antibacterial activity, and photoluminescence property.	Kumar and Girija (2013)
7	Sole fish skin	Collagen	• The best conditions yielded a maximum collagen yield of 19.27 0.05 mg/g of fish skin. • SDS-PAGE was used to determine that the extracted collagen was the type I collagen.	Arumugam et al. (2018)
8	Marine shell waste	Hydroxyapatite microspheres	• Prepared Hydroxyapatite microspheres have a high specific surface area and an opposing surface potential. • Hydroxyapatite microspheres were used to adsorb Congo red (CR) in solution.	Wang et al. (2021)
9	Outer skin waste of *Loligo uyii*	Type V like collagens	• The estimated net yield of acid-soluble collagen from *L. uyii* is 10.54% • When pepsin was used to break down the leftover material, 31.16% soluble collagen was found.	
10	Scales of Tilapia fish (*Oreochromis mossambicus*)	Hydroxyapatite and chitosan composite scaffold	• Scaffolds made of a mix of hydroxyapatite and chitosan were very good at taking heavy metal ions out of waste water.	Liaw et al. (2020)
11	Shrimp shell waste	Wheat gluten based-bioplastics	• Compared to a wheat gluten-based bioplastic without shrimp shell loading, the structural rigidity of the wheat gluten composite with 2.5 wt percent of shrimp shell powder was twice as high.	Veeruraj et al. (2012)
12	Shells of the marine crab (*Portunus sanguinolentus*)	Chitosan	• The extracted chitosan was shown to be anti-virulent and antibiofilm.	Rubini et al. (2018)
13	Carapace (exoskeleton)	Chitosan	• An orthorhombic structure with 30% crystallinity, like shrimp chitosan, was found	Águila-Almanza et al. (2021)
14	Shrimp waste (*Penaeus merguiensis)*	Chitin & chitosan	• Chitin was turned into chitosan using the microwave, an autoclave, and old-fashioned methods • The autoclave method gave the highest yield (87%) of the three	Sedaghat et al. (2017)
15	Cuttlefish-bone biowaste	Mayenite-embedded Ag_2CO_3 nanocomposite	• AgC@m-M is a strong photocatalyst and a good agent for recovering waste oil.	Darwish et al. (2021)
16	Shrimp waste	Chitin & chitosan	• Chitosan was good at fighting free radicals	Sedaghat et al. (2016)
17	Wastes of Persian Gulf shrimp	Chitosan	• It was found that 19.47% of the chitosan preparation had the highest degree of deacetylation (89.34%) and the highest molecular weight (806,931 Da).	Nouri et al. (2016)
18	Larvae of blowfly (*Chrysomya megacephala*)	Chitosan	• Chitosan was an excellent antioxidant, with an IC50 value of 1.2 mg/ml.	Song et al. (2013)
19	Eggshell biowaste	Hydroxyapatite	• The parameters for making nanohydroxyapatite from eggshell biowaste were shown using a microwave method on a lab scale and a pilot-scale microwave reactor.	Muthu et al. (2020)
20	*Cirrhinus mrigala* fish scale wastes	Nanostructured hydroxyapatite crystalline powders	• Nanostructured hydroxyapatite crystalline powders made from waste fish scales from *Cirrhinus mrigala* showed good biocompatibility. • It is a possible alternative biomaterial for many medical uses.	Sathiskumar et al. (2019)
21	Eggshells	Hydroxyapatite	• Hydroxyapatite was able to kill bacteria and stop biofilms from forming.	Umesh et al. (2021)
22	Eggshell	Hydroxyapatite	• The study showed that using used eggshells as a source of calcium along with microwave irradiation was an excellent way to make nano-hydroxyapatite particles.	Goh et al. (2021)
23	Municipal food waste	Bioplastic polyhydroxyalkanoates (PHA)	• PHA can work better than polyurethane made from fossil fuels • PHA made from first-generation biomass (such as sugarcane and maize) is better for the environment and costs society (four times lower impacts and eight times lower costs than polyurethane).	Andreasi Bassi et al. (2021)
24	The organic fraction of municipal solid waste	Polyhydroxyalkanoates (PHAs),	• The amount of biodegradable PHAs found in the organic part of municipal solid waste was 40 g/kg.	Ebrahimian et al. (2020b)

Table 2 (*continued*)

S.L No	Name of biowaste	Prepared biomaterials	Key findings	Reference
25	Rice husk waste	Pure silica	• The mean quality of extracts of silica obtained in various techniques varied from 84.81 to 99.66 wt percent. • When the greener method was used to make silica, it was very pure, with a surface area of up to 625 m^2/g.	Azat et al. (2019)
26	Rice husk, bamboo leaves, sugarcane bagasse, and groundnut shell	Silica nanoparticles	• The amount of silica found in different places ranged from 52% to 78%.	Vaibhav et al. (2015)

composed of some imperfectly spherical shells of black carbon layers separated by roughly 3.36 (Å). XPS and elemental studies revealed that the graphitic layers were doped with O- (6%−15%) and N-atoms (3%−15%), resulting in C═O and -O−C(O)O- groups and N-bearing aromatic rings, respectively. The electrical conductivity of these materials was 4.61×10^{-1} S m^{-1} which is on par with that of pure graphene powder and is especially noticeable at 1000 °C. As a second illustration, aqueous AcOH and superparamagnetic iron oxide nanoparticles (SPIONs) were mixed with collagen isolated from raw cowhide trimming waste. Following moderate ignition (401 °C, 12 h) before freeze-drying, the collagen fibrils rearranged with the nanocrystals to produce a sponge-like, extremely porous interconnecting substance (41 °C, 18 h) (Ashokkumar et al., 2016).

Since the inclusion of SPIONs into the matrix material did not affect the collagen threefold helix conformation, the distinctly different 3D morphology of the composite compared to a natural collagen sponge can be attributed to the potent interactions of the two components. The increased proliferation of model cells (293T) demonstrated that adding SPIONs to the collagen sponge increased its dimensional integrity and made it biocompatible. Furthermore, adding SPIONs significantly improved collagen's macromolecular structure and cell viability (Xu et al., 2019).

5. Economic, environmental, and health effects of biowaste valorization

5.1. Economic impacts

Reduced capital costs are an essential aspect of successful economic and business models. These can be achieved in two ways: (a) by manufacturing high-value goods from zero-cost materials; or (b) by employing zero-waste production techniques, eliminating the need for costly waste disposal. Since biowastes can be valorized, they can be used as inputs in other industries, fostering a mutually beneficial relationship (Baldassarre et al., 2019). As a result, businesses can improve their image among consumers and investors while also reducing biowaste production (Barros et al., 2021). Closing material and energy consumption cycles during product design improves the supply chain, logistics, and manufacturing operations. When resources and goods enter a circular system, better, more cost-effective strategic planning is possible. Using environmentally friendly solutions and sustainable energy and transitioning from a linear to a CE model can help industries improve their competitiveness, revenues, job creation, and creativity. Several industrial aspects must be considered when idealizing agro-industrial recyclable waste. These include increasing the technical proficiency of interested parties through (i) the classification and proper repository design of biomass resources for processing plants, (ii) the assessment of extraction efficiency relying on the organic composition of feedstocks, and (iii) the assessment of the retrieval procedures to obtain ample supply while preventing potentially harmful environmental pathways. Companies that embrace more circular methods save money in the short and long term. These savings include reduced costs for raw materials, waste disposal, and resource recovery projects.

5.2. Environmental and health impacts

Adopting circular economy-based approaches to commodifying biowaste to manufacture biomaterials could contribute to various objectives, including minimization of biohazardous material, upcycling into high-value goods, and environmental protection (Omran et al., 2018). This switch is essential to reduce greenhouse gas emissions from treating such biowastes using conventional methods and safeguarding the environment from the harmful chemicals and gases produced in landfilling or incineration processes. Every stage of a product's life cycle, including manufacturing, consumer use, and final disposal, has unique environmental effects. Smart manufacturing and digital transformation facilitate environmental performance (Olah et al., 2020). Despite the previously mentioned positive environmental effects of converting agro-industrial biowastes into biomaterials, it is critical to study, measure, and comprehend the risk to public health associated with using of such nanomaterials. Nanotoxicology is important for analyzing bio-nano interactions (Tarrahi et al., 2021). Nanotoxicological investigations can tell us if and to what extent green nanomaterials (NMs) threaten the environment and living things, even though their properties are similar to those of chemically and physically manufactured NMs (Hu et al., 2016). The “reduction, refinement, and replacement (3Rs)” philosophy is currently used as an alternative to *in vivo* animal experimentation. This philosophy is implemented to avoid unethical practices and overcome the limitations of animal testing (Huang et al., 2021).

6. Discussion

We all know that converting biowaste into value-added products has always been difficult. Waste availability, purity, and composition have long been contested in commercial or large-scale production. Biowaste is a significant source of environmental contamination and a massive repository of valuable resources due to the high amount of organic and biodegradable components it contains that may be repurposed. The conversion of biowaste into resources *via* biorefinery is an unavoidable development that could help reduce carbon emissions and the rising environmental problems associated with solid waste. This paper investigates the current achievements and potential trends in the use of commonly available biowaste to produce essential biomaterials (such as collagens, hydroxyapatite, bioplastics, chitosan, chitin, polyhydroxyalkanoates, pure silica, *etc.*). To achieve the goal of a circular bioeconomy, various techniques for converting biowaste into high-value resources are required. Furthermore, the use of recycling technologies and incorporating bioconversion to improve process performance are critically examined. Because data on biowaste generation from public research is currently insufficient, it is necessary to identify, quantify, and investigate the periodicity of these residues to determine which are the major products for their

treatment toward value-added products (Kee et al., 2021; Srivastava et al., 2023).

The fundamental understanding of mechanisms is critical and necessary to ease the transition of biowaste valorization technology from lab-scale to pilot-industrial scale. However, due to the complexities of biowaste feedstock, determining the paths and processes of the above-mentioned technologies for conversion remains a challenge. Furthermore, many technical limitations in conversion procedures prevent large-scale biowaste valorization. For example, the pyrolysis process requires a long heating time, yet uneven heating may affect biochar quality. Biowaste for pyrolysis should have dry, unmixed, and uniform physical and chemical qualities. In reality, most biowaste is a mix of wet domestic and commercial wastes.

Furthermore, the thermochemical conversion process generates tar, which reduces the system's overall efficiency. In addition, thermochemical conversion processes such as pyrolysis emit gaseous byproducts that harm the environment. More work needs to be done in the biochemical approach to improve the performance of enzyme activity and feedstock properties. Because of the heterogeneous character of municipal organic solid waste, its larger particle size and refractory woody components are very difficult to valoriz (Cheng et al., 2020; Kee et al., 2021; Srivastava et al., 2023).

7. Conclusions and future direction

This article thoroughly explains the underlying implications of biowaste's potential as a resource in a circular economy system. Additionally, we have demonstrated that the circular economy has full potential regarding sustainability, environmental, and social development. We assessed the biowaste used as a resource feature and employed several treatment methods worldwide to develop various biomaterials. A systematic approach to improving biowaste circularity that benefits society has also been presented. The economic and environmental effects of converting biowaste into valuable biomaterials are analyzed. Handling biowastes is a complex process that requires the cooperation of governments, rules, regulations, stakeholders, corporations, products, consumers, and public opinion. A multidisciplinary approach can make these processes sustainable, leading to a zero-waste economy and a more environmentally friendly bio-based society. Achieving this objective necessitates cross-industry and public–private collaboration to devise a plan with significant economic, social, and environmental benefits. In the future, the primary goals must be to raise public awareness that the rising global population and quality of life contribute to an increase in waste production, as well as to demonstrate how advanced biowaste valorization can be used as an input into other processes to recover and reuse specific biomaterials. Life cycle assessment (LCA)-based approaches must additionally be advanced to improve the sustainability of biowaste management systems. Furthermore, there are several significant obstacles related to LCA system boundaries that continue to present challenges for biowaste management. In that situation, LCA researchers were asked to tackle significant issues, such as the environmental impact assessment of the unorganized waste industry or the informal biowaste sector. The waste-to-wealth concept seeks to create a future sustainable lifestyle in which waste is valued for its environmental benefits and the development of new technologies, livelihoods, and jobs. Physical, chemical, or biological processes allow biowastes to undergo drastic changes that result in various valuable products and materials. In light of this potential, several positive aspects of the transition to a circular economy should be evaluated, including developing novel products, analyzing alternative company and market structures, and encouraging consumers to change their habits and routines toward waste management. However, because of the highly heterogeneous nature of biomass waste, it is difficult to imagine the type of final or categories of end-products and specify their properties, making developing valorization strategies challenging. Many of these studies, though, are still in their early stages and must surpass the discovery of a new method or technique to include an in-depth evaluation of both technological and socio-ecological constraints, such as the simplification of detoxification guidelines, harvesting yields, upscaling concerns, caloric expenditure and expense, pollutant impacts, and the general acceptance and acceptance of new technology development. The proper valorization and utilization of biowastes generated from diverse sources safeguard the environment and contribute to creating a more sustainable society.

Author contributions

Conceptualization, B.M., and Y.K.M; Data curation: H.S, B.M., C.N.R, R.Y., S.K.M., and S.D.M.R; Writing—original draft preparation, B.M., Y.K.M., C.N.R, S.D.M.R; Writing—review and editing, H.S., C.N.R., R.Y., and S.K.M.; Visualization, H.S, Y.K.M., and C.N.R. All authors have read and agreed to the published version of the manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Energy generation from bioelectrochemical techniques: Concepts, reactor configurations and modeling approaches

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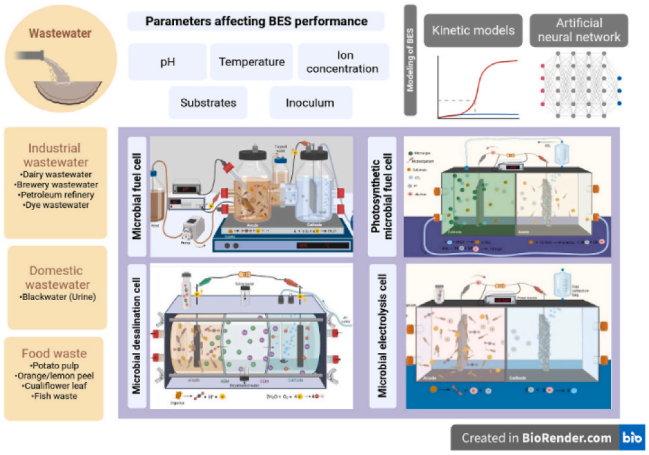
HIGHLIGHTS

- Different types of bioelectrochemical systems (BESs) used for waste treatment are discussed
- Parameters influencing the performance of BESs are listed and examined
- Artificial neural network models used to evaluate the performance of BESs are presented
- Microorganisms involved in waste degradation and future trends in BESs are highlighted

GRAPHICAL ABSTRACT



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ABSTRACT

The process industries play a significant role in boosting the economy of any nation. However, poor management in several industries has been posing worrisome threats to an environment that was previously immaculate. As a result, the untreated waste and wastewater discarded by many industries contain abundant organic matter and

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other toxic chemicals. It is more likely that they disrupt the proper functioning of the water bodies by perturbing the sustenance of many species of flora and fauna occupying the different trophic levels. The simultaneous threats to human health and the environment, as well as the global energy problem, have encouraged a number of nations to work on the development of renewable energy sources. Hence, bioelectrochemical systems (BESs) have attracted the attention of several stakeholders throughout the world on many counts. The bioelectricity generated from BESs has been recognized as a clean fuel. Besides, this technology has advantages such as the direct conversion of substrate to electricity, and efficient operation at ambient and even low temperatures. An overview of the BESs, its important operating parameters, bioremediation of industrial waste and wastewaters, biodegradation kinetics, and artificial neural network (ANN) modeling to describe substrate removal/elimination and energy production of the BESs are discussed. When considering the potential for use in the industrial sector, certain technical issues of BES design and the principal microorganisms/biocatalysts involved in the degradation of waste are also highlighted in this review.

1. Introduction

The energy demand to meet industrialization and population growth is expanding day by day and is considered a primary global threat. The energy requirement is a major driving force of the global economy (Mullai et al., 2022; Jåstad and Bolkesjø, 2023). The economic activities are directly influenced by limiting energy use. The amount of energy needed to lift developing countries out of poverty is tremendous. The probabilities of elevating energy needs are mostly questionable (Srikanth et al., 2016a; Yogeswari et al., 2019; de Fouchécour et al., 2022). Simultaneously, with the global increase in energy demand, waste generation and pollution-related problems are also rising globally. For example, the excessive production of waste has created waste management issues, such as landfill space shortages, environmental contamination, and resource depletion. To address these issues, societies and governments are employing technologies for waste minimization, recycling, and waste-to-energy conversion (Akinyemi et al., 2019; Duarte et al., 2019; Gredilla et al., 2019; Oliveira et al., 2019a, 2019b, b; Dutta et al., 2020; Saikia et al., 2020; Silva et al., 2020a, 2020b). Therefore, sustainable waste management and energy practices are necessary to establish a society that is more environmentally conscious and resource-efficient. This includes reducing waste production, increasing recycling rates, shifting to renewable energy sources, and promoting energy-efficient technologies.

Environmental experts have tried in many ways to derive energy from the waste components, viz., biogas from anaerobic digestion, electricity generation along biosolids incineration, energy revival from biogas utilization, and energy recovery from biosolids incineration. The biogas that is obtained through the treatment of various wastes can bae an efficient source of fuel in a process industry as well as a sustainable way of effluent treatment (Mullai et al., 2018). In this aspect, different reactors have been tested at the lab-scale and pilot-scale (Rossi and Logan, 2022; Tsapekos et al., 2022). There are studies that show high rates of methane production (Mullai et al., 2020) and treatment of wastes with different reactor setups, such as as anaerobic sequential batch reactor (Arreola-Vargas et al., 2016) , anaerobic membrane bioreactor (Moideen et al., 2023), continuous stirred tank reactor (CSTR) (Wei et al., 2022), upflow anaerobic sludge blanket reactor (UASB) (Wu et al., 2020a), anaerobic fluidized bed reactor (de Souza Dornelles et al., 2020), anaerobic expanded granular sludge bed reactor (Granatto et al., 2021) and continuous hybrid fixed bed anaerobic filter reactor (Ahmed et al., 2021).

It has been a long decade before renewable energy production in the form of methane from the solid and liquid waste streams has been established via anaerobic digestion. Energy generation from the waste streams concurrently supports the power needs, inclusive of pollutant removal from the effluent. The hunt for a sustainable solution to overcome energy demand and waste remediation inspired the technological evolution of energy recovery from waste (Yang et al., 2022). Bioelectrochemical systems (BESs) are energetic entities and serve as an ideal platform for the generation of valuable energy sources from organic waste through chemical energy conversion, viz. electric power, hydrogen fuel cells, and value-added products. It utilizes microbes as a catalyst, and common microbial-electrochemical reactions are engaged in this system, which facilitates both the oxidation and reduction reactions. Electrically active bacteria can be assessed as catalysts (Bajracharya et al., 2016; Sambavi et al., 2020). The summary of the outcome of the BESs in terms of effluent treatment efficiency and electrochemical performance is listed in Table 1.

This review seeks to identify and discuss the various factors influencing the efficacy of BESs for waste and effluent treatment. Besides, the evaluation and prediction of the performance of BESs using artificial neural networks has been discussed because this topic has received a lot of interest from the research community. In addition, the treatment of a wide variety of wastes and wastewaters, as well as the function of microorganisms and biocatalysts in the process of waste degradation in BESs, are both covered in this review paper.

2. Configuration of bioelectrochemical systems

The configuration of BESs based on their application is majorly grouped into microbial fuel cell (MFC), microbial solar cell (MSC), microbial electrolysis cell (MEC), and microbial desalination cell (MDC) (Pant et al., 2012). The detailed methodological description and concepts of MFC, MSC, MEC, and MDC are discussed as follows (Figs. 1–4).

2.1. Operation of BESs

Organic substances are cracked up in the presence of microorganisms , and it changes chemical energy into electrical energy. During this organic oxidation, the electrons and protons are originated from

Table 1
Summary of removal efficiencies and electrochemical performance of BESs for different types of wastewaters (Adapted from (Ramírez-Vargas et al., 2018).

Source of wastewater	Removal efficiencies	Electrochemical performance
Diluted swine wastewater	COD: 81% Total nitrate: 45% NH_4: 53%	Coulombic efficiency: 1.2% Power density: 87.79 mW/m^2
Urban wastewater	COD: 61% NH_4: 60%	Current density: 138.8 mA/m^2 Power density: 14.5 mW/m^2
Synthetic nitrate containing wastewater	COD: 57% NO_3: 80%	Current density: 53.74 mA/m^2 Power density: 8.08 mW/m^2
Oil contaminated wastewater	COD: 73% TOC: 57% Oil: 95%	Power density: 102 mW/m^2
Nitrobenzene containing wastewater	COD: 78% NB: 92%	Current density: 8.52 mA/m^2 Power density: 1.53 mW/m^2

microbes. It is known that oxidation occurs in the anode and reduction in the cathode of an electrolytic cell. The formed proton from the anode region passes through the membrane and reaches the cathode region for energy production. The cathode (electron acceptor) receives the generated electrons from the anode via the external electric circuit. Commercialization of MFC for pollutant removal and sustainable energy production is today's emerging technology. The operational advantages of MFC are listed as follows: (i) suitable for even low pollutant levels, (ii) different substrate materials can be used, (iii) flexibility in modifying designs, operating conditions, and catalyst selection towards maximizing the removal efficiency, and (iv) other advantages such as the production of sustainable energy from waste matrices, low impact on the environment, decrease of greenhouse gas emissions, potential for water reuse, and the possibility to be integrated with other technologies (Fig. 1) (Babanova et al., 2020; Sambavi et al., 2020; Sonawane et al., 2022).

A hybrid system of electrochemically active microbes and photosynthesis using solar energy is utilized for the generation of a green source of energy, i.e. methane, ethanol, and hydrogen, is commonly called as MSC (Fig. 2) (Strik et al., 2011; Wang et al., 2014a). The hydrogen generation from acetate, fermented end products by electro-hydrogenizes is performed in MEC. In the current modern technology, different bacterial cultures are being employed in this process, which releases electrons to the anode. The oxygen reduction at the cathode ensures electricity generation while in the absence of oxygen, the cathodic reaction occurs (Fig. 3) (Kadier et al., 2016; Fadzli et al., 2021). Thus, MDC can concurrently generate energy and remove the contaminants from different waste streams using active biocatalysts (Fig. 4) (Saeed et al., 2015; Al-Mamun et al., 2018).

3. Parameters affecting the performance of BESs

The different physicochemical and biological characteristics of the environment in which the BESs are operated can have an effect on their performance.. The primary parameters are the source, initial pH, and initial concentration of the pollutants. Environmental properties such as the oxygen level, moisture content, and temperature are also influencing its performance. The combination of electrodes, types of anode, and cathode are the general parameters that always influence the efficiency of electrochemical reactions. In brief, when designing and operating a BESs, the following parameters should be taken into consideration: substrate type and concentration, pH and temperature, the composition of the microbial community, electrode material and design, hydraulic retention time (HRT) and flow rate, cell configuration and stack arrangement, external resistance and voltage, characteristics of the ion exchange membrane, start-up conditions and an acclimation period, anode and cathode surface area, and the availability of nutrients.

The growth of the microbes could be promoted by the addition of suitable external nutrient sources like vitamins, glucose, and suitable substrates such as sucrose, acetate, etc. The external resistance and electron transfer activities could influence the contaminants removal and power generation in BESs (Zhang et al., 2019b).

3.1. pH

The primary parameter for the existence of microorganisms is the optimum pH range. The pH gradient between the electrodes influences the growth and effectiveness of microorganisms. The pH outside the optimum range will abolish microbial activity. The charge carried by the microbes may vary due to the pH change, which disturbs the biochemical reactions. Spotting the optimum pH for the survival of both electrogenic microorganisms and degrading microorganisms is hard. The pH of the medium directly controls the generation of electrons and protons, thus affecting the generation of electricity. A higher pH favors the growth of methanogens and reduces the proton formation. Inversely, a lower pH close to neutral hinders methane production. The pH primarily limits substrate bioavailability (Vu and Min, 2019). The anode pH also significantly impacts the performance of MFC and MEC. For example, a pH between 5.0 and 6.0 results in a more substantial hydrogen generation rate, up to roughly 8 m^3 $H_2/m^3/d$, whereas a pH between 6.5 and 7.5 correlates with considerably greater power densities, up to about 1200 mW/m^2 (Simeng and Gang, 2018).

3.2. Temperature

Unlike chemical reactions, biochemical reactions are extensively temperature sensitive. Every microbe has a different sensitivity profile to the optimum temperature at which it can exhibit its maximum

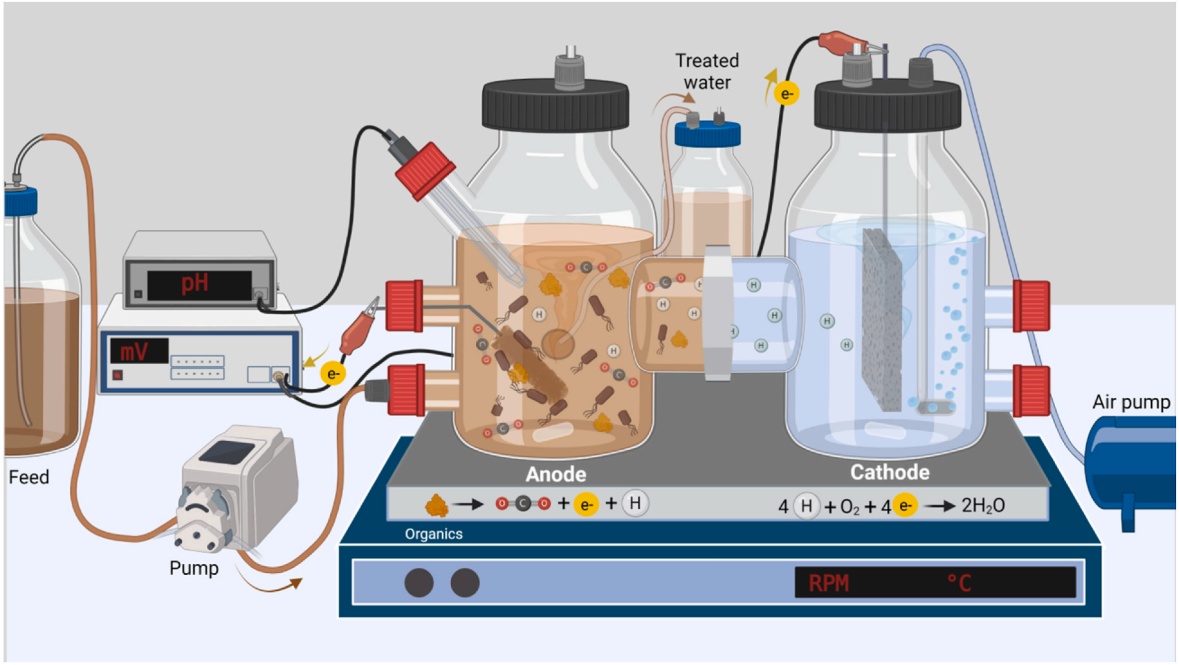

Fig. 1. Schematic of a microbial fuel cell (MFC) assembly at the lab scale.

microbial activity. Generally, it ranges between 35 °C and 40 °C. The promotion of electricity generation is usually observed in this condition. Based on the statement of Arrhenius's law, the increase in temperature ends with escalated power generation as an output. The performance of BESs also increases with an increase in temperature, but the reverse trend was observed beyond the optimum condition. The reason explained is that the microbial enzyme structures are weakening, which also alters the cell activity. Along with power generation and pollutant degradation, the high temperature could stimulate the evolution and reproduction of non-electrogenic microorganisms that compete with electrogenic organisms and improve performance efficiency. Generally, BESs with a mixed inoculum operate well at 40 °C. Still, considering the unfavorable outcomes of elevating the temperature, it is suggested to kick off the system with high heat and then run at a comparatively low temperature. Mineral wool and foam (as insulating materials) and solar energy are used to inhibit the impact of higher temperatures on the degradation of the physical-chemical properties of the substrate (Lu et al., 2016).

3.3. Ion concentration

Three parameters that affect the performance of bioelectrochemical systems (BESs), especially microbial fuel cells (MFCs) and microbial electrolysis cells (MECs), are the ion concentration, the composition of the wastewater, and the conductivity. These three parameters are closely related to each other and can have a substrantial impact on the performance of BESs. Increasing the ion concentration in the system directly diminishes the internal resistance and promotes electron transfer and electricity production. The presence of ions, particularly those that are electrochemically active (e.g., ions that can engage in redox processes), can facilitate the transfer of electrons from microbes to the electrode surfaces. Increases in both the concentration and conductivity of ions can improve or enhance the efficiency of electron transfer, which can then contribute to increased energy generation in BESs. Besides, an optimum level of ion concentration favors the system's performance. On the other hand, when the ion concentration exceeds limits, the system becomes toxic to the growth of microbes and reduces power generation due to insufficient water level. Metal ions like Cu^{2+}, Na^{+}, K^{+}, and Zn^{2+} play a major role in the growth of microorganisms. The resistivity of the microorganisms is measured to provide the appropriate environmental conditions for the satisfactory performance of BESs (Hassan et al., 2021).

3.4. Soil moisture content

Microorganisms use water as a medium for the transfer of materials like nutrients, ions, etc. The alteration in the soil water level impacts the concentration of nutrients (C, H, and N sources) by diluting them, resulting in a decrease in bioactivity. On the other hand, the increase in moisture level enhances the solubility of hydrophilic contaminants into a water-soluble state, which stimulates their degradation ability by microbes. The high moisture content also influences the ion exchange mechanism and the effective utilization of substrate in the solid media. The pH of the soil turns neutral, and then it calms down the higher salinity level in the soil (O'Brien et al., 2010).

3.5. Substrates

The substrate finalizes the functions of microorganisms. The substrate types and concentrations determine the survival and growth of the organisms. The contaminants present in the effluent and the nutrient sources are significant parts of the substrates. BESs have been applied in wastewater treatment in various industries, such as the pharmaceutical, textile, dairy, oil and petrochemical, agro-food processing, smelting industry, etc., among others. Several different process industries can get benefits in the areas of waste management, energy recovery, and environmental sustainability by integrating BESs into their operations. However, it is essential to keep in mind that the implementation of BESs in highly polluting sectors (for example, those with high COD, SS, oil, fat, and grease levels) may involve difficulties in terms of the optimization of the process, the scalability of the system, and its economic feasibility for full-scale operations. The composition of the substrates,

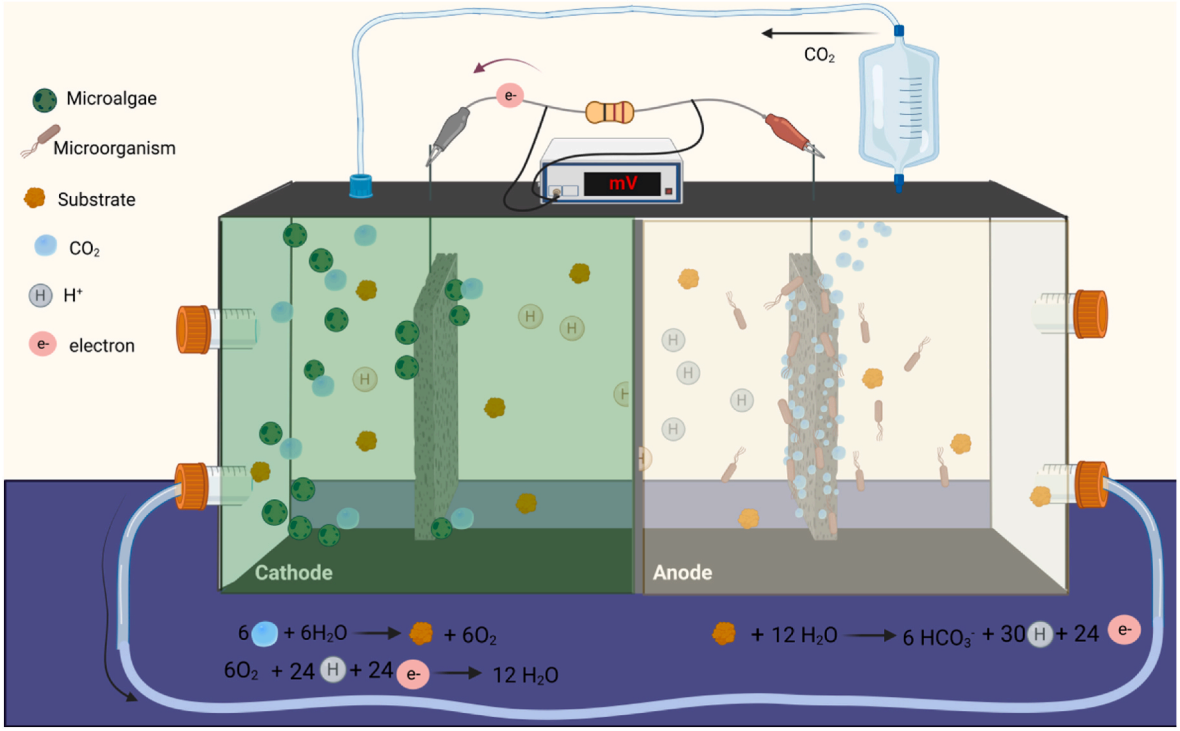

Fig. 2. Schematic of a photosynthetic microbial solar cell (MSC).

especially the amount and source of carbon, promotes the adoption abilities of the microorganisms with contaminants (Morin-Crini et al., 2022a). Reports of previous studies have revealed that the carbon, sourced from glucose, escalates the performance of the BESs more than the acetate source. It is well understood that a high level of pollutant concentration can provide more carbon resources to produce electricity (Wu et al., 2020b).

3.6. Inoculum

Electrogenic microorganisms are preferred in BESs. Electrogenic microorganisms are bacteria that have the unique ability to transmit electrons created during their metabolic activities to external solid conductive materials. This feature distinguishes electrogenic microorganisms from other types of microbes, and they are currently being used in BESs. Both pure microbial strains and heterogeneous bacterial strains are utilized in the treatment process. It was noted that the electron transfer efficiency is higher when the pure microbial strain was applied than when the mixed strains were used. But the treatment cost increases when pure strains are involved due to the maintenance of a sterile environment. Inversely, the mixed microbes are emphasizing the declining internal resistance inside the BESs. The difference in types of microbes promotes the degradation of contaminants and concurrent power generation. In brief, handling the bacteria in the BESs is simple, economical, and efficient. The composition of the inoculum determines the performance of the BESs. To promote reactor execution, the inoculum was taken from the other reactor effluent, which has enormous active electrogenic bacteria, so that degradation will be aided (Jadhav and Ghangrekar, 2020).

3.7. Reactor design parameters

Along with the environmental and effluent parameters, the design configuration of the reactor also influences the performance of the BESs. This includes the type of anode and cathode material of construction, the distance between them, electrical conductivity, aeration, and the number of chambers in the system. In most cases, electrons are produced by microorganisms while they are growing in the anode zone, and the cathode region functions as an electron acceptor when it obtains a sufficient amount of oxygen. However, because the single chamber system does not need aeration, the operational cost is significantly reduced (Liu et al., 2017).

Various types of electrode materials have been researched and designed recently to increase the efficiency of MFC and MEC while lowering the price of the reactors. Carbon paper, carbon cloth, and graphite brush are the three most commonly used carbonaceous electrode materials. Carbon paper has a surface that is generally smooth and thin, firm, yet slightly fragile. For the production of hydrogen in MEC and electricity in MFC, carbon cloth electrodes are by far the most efficient. The performance of reactors that utilise carbon paper as electrodes is only slightly greater than the performance of reactors that use graphite brush (Simeng and Gang, 2018). Previous studies have ascertained the maximum power output by varying the electrode materials, i.e., (i) anode: carbon felt; cathode:carbon cloth coated with a PbO_2 layer; maximum power output (mW/m^2): 2500 (Estrada et al., 2018) (ii) anode: polyvinyl alcohol (PVA) coke and graphite rod; cathode: carbon cloth; maximum power output (mW/m^2): 17.6 (Liu et al., 2018) (iii) anode: Fe_2O_3 polyaniline dopamine and carbon felt; cathode: carbon felt; maximum power output (mW/m^2): 3184 (Jian et al., 2020) (iv) anode: sacrificial aluminum, graphite, or activated carbon; cathode: conductive membrane with Fe/Mn/O catalyst; maximum power output (mW/m^2): 2250 (Wang et al., 2020).

The results from previous studies have demonstrated that single-chamber and double-chamber reactor configurations produce energy differently. While single-chamber MECs could produce more biohydrogen, double-chamber MFCs typically generate more power. Two-chamber systems present a greater challenge and would generate less electricity in MFC due to their high electrical resistivity. Besides, two-chamber systems are used more frequently due to their simplicity and stability (Liu et al., 2005). Table 2 lists the advantages and disadvantages of different BESs.

4. Treatment of various wastes and wastewaters

In the current scenario, with the growth in population and globalization, there is a dramatic increase in the amount of waste generated. This waste generally includes food waste, domestic waste, agro-waste, and water streams that contain various pollutants such as pharmaceutical pollutants, synthetic dyes, heavy metals, and many others.

Food waste is generated from a variety of sources, such as

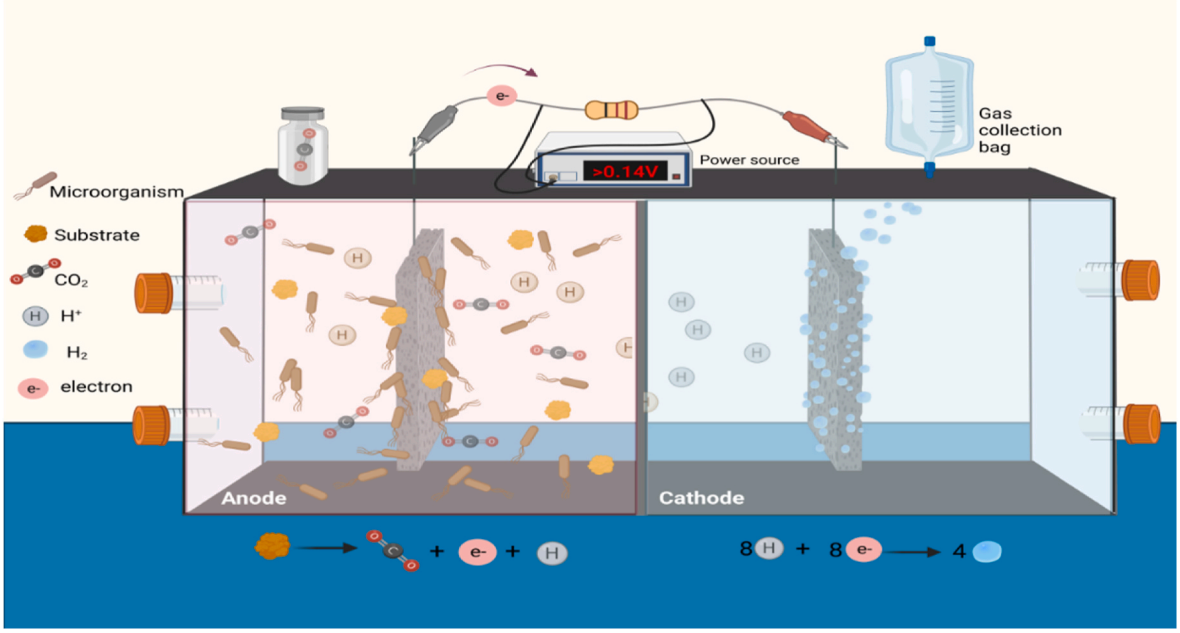

Fig. 3. Schematic of a microbial electrolysis cell (MEC).

households, restaurants, and so on, and mostly consists of high molecular weight polymers like cellulose, protein, fats, and other organic matter (Li et al., 2016). For MFC's performance using food waste, several studies have been done; the maximum closed-circuit voltage and power density were 775 ± 21 mV and 422 mWm^{-2}, respectively, and COD removal of 69 ± 18% was observed with degradation of carbohydrate (88 ± 5%), proteins (76 ± 9%), and total nitrogen (71 ± 8%) (Elhenawy et al., 2022). There are also studies that use food waste as a substrate and reduce lead ions in wastewater using MFC, and the maximum power density was observed at 41.58 mW/m^2 with a 95% removal efficiency of lead ions (Yaqoob et al., 2022). Zafar et al. (2023) used two MFC designs to minimize solid fruit waste, and it was found that the two-stage MFC removed solids up to 95% and total COD of 83%, compared to the single-stage MFC. A power density of 221 mW/m^2 was reached in 30 days using the two-stage anaerobic up-flow leachate reactor.

Industries such as printing, textile, and leather release numerous pollutants that cannot be degraded easily (Slama et al., 2021). Azo dyes, which are widely used in textile industries and are one of the major pollutants in wastewaters, can be used as electron acceptors at the cathode. MFCs are able to decolorize the widespread environmental pollutant, i.e., azo dye (Sun et al., 2011; Li et al., 2021). Huang et al. (2017) investigated the application of MFC with a redox mediator-modified anode, which enhances the decolorization of azo dye and simultaneously generates electricity. A TiO_2-coated photocathode, termed a photocatalytic microbial electrolysis cell (PMEC), was developed to degrade methyl orange (MO) and simultaneously recover hydrogen using UV irradiation. It was observed that the decolorization efficiency varied from 98% to 76% within 12 h, with an initial concentration of MO of 50–300 mg/L, at a voltage of 0.8 V. The major intermediates of MO, such as N, N-dimethylaniline, and sulfanilic acid, were further degraded by OH (Hou et al., 2017).

Over the last few years, pollutants like antibiotics, antidepressants, steroids, hormones, drugs, and chemical residues from pharmaceutical industries in the aqueous environment have been labeled as environmental hazards (Popa et al., 2014; Zhang et al., 2015; Huang et al., 2022; Saidurrahman et al., 2022). Pharmaceuticals must be removed from effluent in order to protect aquatic ecosystems and human health. Governments, researchers, industries, and communities must work together to develop strategies for preventing pharmaceutical contamination, enhancing effluent treatment, and ensuring the long-term sustainability of water resources (Ahmed et al., 2015). The most widely released antibiotics include nitroaromatic antibiotics, chloramphenicol, paracetamol, and penicillin, which cause numerous health issues in animals and humans. Researchers studied the degradation of antibiotics, paracetamol, and chloramphenicol in BES. Zhang et al. (2017) explained the use of MFC in the degradation of chloramphenicol; it exhibits 84% degradation within 12 h. From the various studies, it has been observed that there is a more rapid biodegradation rate in MFC. Also, a maximum generation of 2.01 W/m^3 and 168 mA/m^2 of power and current densities, respectively, was found in a study that used paraboloid graphite-based MFC (Rashid et al., 2021).

One of the most toxic refractory organic pesticides, hexachlorobenzene (HCB), is toxic to the environment and also to living beings. There are many remedial techniques developed to remove this contaminant from soil (Morin-Crini et al., 2022b). To remove this contaminant, soil MFCs were constructed at the top of the contaminated soil. Cao et al. (2015) investigated the performance of HCB degradation and electricity generation in soil MFC. HCB was degraded through the reductive dechlorination pathway in the soil MFC under anaerobic conditions. The removal efficiency obtained for HCB in soil MFC was 71.15%, which could be promoted by the use of anode-promoted electrogenic bacteria.

Additionally, various kinds of wastewaters are treated in MFC. As brewery wastewater was being treated using the inoculated MFCs, and they able to do so with a power density of 350 mW/m^2 and a maximum

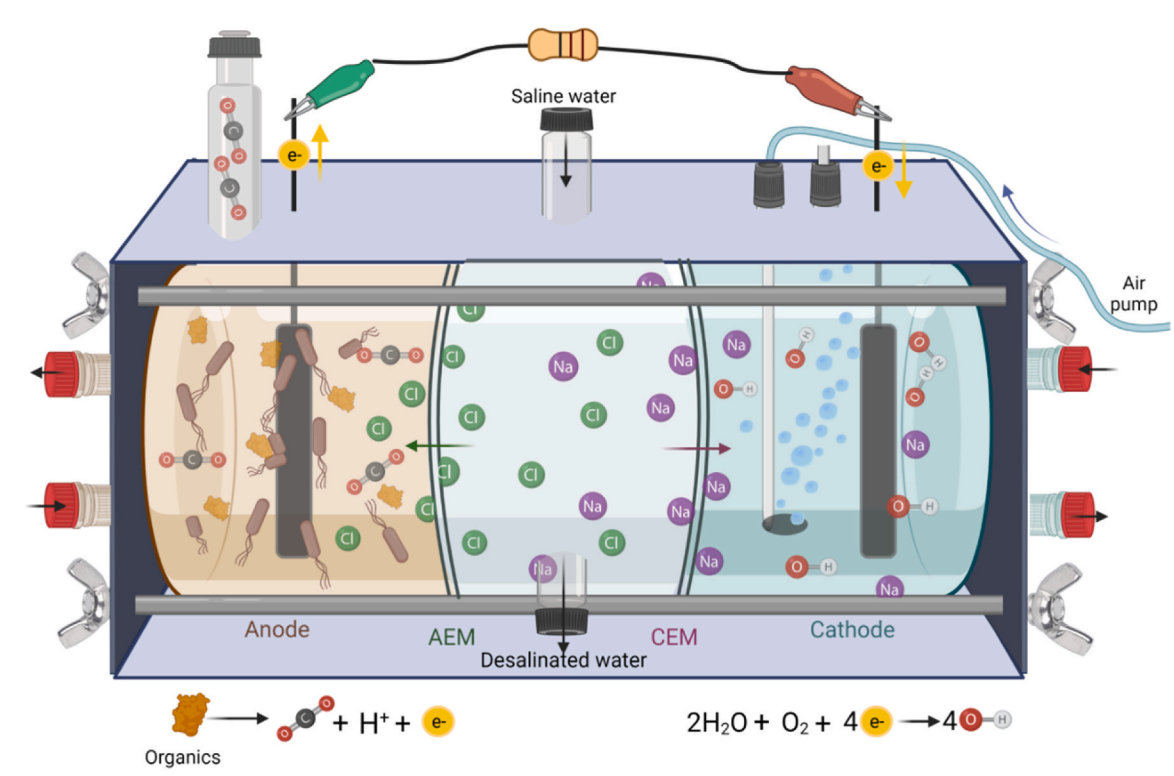

Fig. 4. Schematic of a microbial desalination cell (MDC).

Table 2
Advantages and disadvantages of different BESs.

Types of BESs	Advantages	Disadvantages
Single-chamber	Simple design, cost-effective, and higher power output	Water administration is difficult and often has low coulombic efficiency because of oxygen diffusion
Double-chamber	Can be operated in batch or continuous mode, and different conditions can be maintained in each compartment	Complex designs and difficult to scale-up
Up-flow mode	Contact between biomass and substrate is accomplished by the influent flow instead of mechanical mixing and is easy to scale-up	The high energy cost for pumping up the fluid, higher resistance, and lower power output
Stacked	Maximum COD removal can be achieved if the MFC units are operated in parallel with proper operating conditions and enhanced current output	Difficult to maintain the same conditions in all the compartments, high cost, and complex designs

COD, biological oxygen demand (BOD), and total dissolved solids (TDS) removal efficiency of 79–83%, 55–67%, and 76–78%, respectively. This shows that brewery wastewater can be treated efficiently to produce sustainable and clean energy (Negassa et al., 2021). Researchers also used rice mill wastewater as substrate, and a maximum power density of 4.3 W/m^3 was obtained for a COD of 2.5 g/L using the system (Raychaudhuri and Behera, 2023). They also found that the Han-Levenspiel model is ideal for describing the correlation between substrate degradation and power density. According to Chauhan et al. (2022), a maximum power density of 7371 mW/cm^3 was obtained during the treatment of tannery wastewater, resulting in an overall treatment efficiency of 85%. In turn, the treated wastewater can be used for various purposes like irrigation, cleaning, and so on. In recent years, the treatment of wastewater using MFC has gained much interest. Currently, researchers are using different types of MFC to treat wastewater based on the number of chambers and mode of operations, such as single-compartment, two-compartment, up-flow mode, and stacked MFC systems (Rathour et al., 2019).

Tables 3 and 4 show different types of BESs for treating various wastes and wastewaters. In conventional methods, various solid wastes are disposed of by composting, land filling, incineration, anaerobic digestion, etc. In recent scenario, these solid wastes were used as potential feedstock for the generation of bioenergy by MFC (Maharjan et al., 2023) It can be clearly seen from Table 3 that food wastes such as composite canteen food waste, lemon peel waste, onion waste, orange peel, pineapple waste, and rice straw waste were able to generate power greater than 100 mW/m^2 (Mohan and Chandrasekhar, 2011; Wang et al., 2014b; Miran et al., 2016a,b; Rojas-Flores et al., 2022). Few research groups achieved a minimum of 60% COD removal even though the produced power was less than 100 mW/m^2 (Karluvalı et al., 2015; Tian et al., 2017; Colombo et al., 2017; Moharir and Tembhurkar, 2018). Other solid wastes, such as municipal solid waste and refractory organic waste, were also considered valuable feedstocks for producing bioenergy by MFC (Karluvalı et al., 2015; Zhang et al., 2019b, Zhang et al., 2019a; Bolognesi et al., 2021).

The results obtained from the different studies revealed that the performance of MFC was lower than ideal due to various factors, including type of microorganisms, type of fuel (substrate), concentration, feed rate, pH, temperature, ionic strength, type of electrodes, proton exchange system, and oxygen for the cathodic chamber (Chang et al., 2023). Furthermore, the performance of MFC was directly affected by the internal resistance due to ohmic losses that occurred during electrochemical reactions. Ohmic losses take place because of electrolyte resistance (anolyte and catholyte) and the proton exchange

Table 3
Summary of the different types of BESs treating various wastes.

Type of waste	Type of BESs	Maximum COD removal (%)	Maximum Power	Coulombic efficiency (%)	Reference
Bakery waste	Two-chamber MFC	–	29.96 mW/m^2	–	Han et al. (2020)
Cassava peel extract	Single-chamber air-cathode MFC	–	155 mW/m^3	11	Adekunle and Raghavan (2017)
Cauliflower leaf waste	Two-chamber MFC	24.7	10.1 W/m^3	–	Maharjan et al. (2023)
Cheese whey	Membraneless single-chamber MFC	96.9	–	2.02	Colombo et al. (2017)
Citrus pulp	Membraneless single-chamber MFC	93.52	–	3.13	Colombo et al. (2017)
Canteen food waste	Single chamber solid phase MFC	76	170.81 mW/m^2	–	Mohan and Chandrasekhar (2011)
Fish waste	Membraneless single-chamber MFC	88.69	–	7.77	Colombo et al. (2017)
Food waste leachate	Two-chamber MFC	65.76	29.23 mW/m^2	14.22	Moharir and Tembhurkar (2018)
Kitchen Waste	Membraneless single-chamber MFC	64.25	–	9.91	Colombo et al. (2017)
Lemon peel waste	Dual chamber MFC	75.8 ± 7.1	371 ± 30 mW/m^2	32.3	Miran et al. (2016a)
Municipal solid waste landfill mature leachate and dairy wastewater	Dual chamber MFC	84.9	~16 W/m^3	<25	Bolognesi et al. (2021)
Municipal solid waste	Tubular microbial fuel cell	52.8± 4.2	47.6 mW/m^2	4.9	Karluvalı et al. (2015)
Onion waste	Single-Chamber MFC	–	595.69 ± 15.05 mW/cm^2	–	Segundo et al. (2022)
Orange peel	Mediatorless MFC	78.3	277.5 ± 5.3 –358.8 ± 15.6 mW/m^2	7.55–15.5	Miran et al. (2016b)
Pineapple waste	Single chamber MFC	–	513.99 ± 6.54 mW/m^2	–	Rojas-Flores et al. (2022)
Potato pulp waste	Single chamber MFC	55.4–68.4	20.4 ± 0.3–32.1 ± 0.5 W/m^3	18–56	Tian et al. (2017)
Refractory organic wastes (phenol)	Photoelectrocatalytic-MFC	96	106.40 W/m^3	27.30	Zhang et al. (2019a)
Rice straw hydrolysate	Single-chamber air-cathode MFC	72 ± 1.7	293.33 ± 7.89 mW/m^2	8.5-17.9	Wang et al. (2014b)

Table 4
Summary of the different types of BESs treating various wastewaters.

Type of wastewater	Type of BESs	Operating conditions	Maximum COD removal	Maximum Power	Reference
Beverage industrial wastewater	Graphite-based truncated conical MFC	COD: 3500 mg/L pH: 6.5 Temp: 28 ± 2 °C	0.841 kg COD/m^3-day	1.14 mW	Nawaz et al. (2020)
Synthetic sugar industry wastewater	Microbial fuel cell	Temp: 25–32 °C	82%	121.39 ± 2.12 mW/m^2	Córdova-Bautista et al. (2020)
Baker's yeast wastewater	Dual chambered MFC	COD:19,500 mg/L pH: 7.5-9.5	91.7%	51.02 mW/m^2	(Abubackar et al., 2023)
Dairy wastewater	Up-flow tubular MFC	OLs: 1.125, 1.650, 2.100 kg TCOD/m^3 Temp: 30 ± 0.5 °C pH: 6.85–6.90	94%	3.5 W/m^3	Marassi et al. (2020)
Copper containing wastewater	Membrane-less MFC	COD: 1400 ± 100 mg/L pH: 3.0–7.0	96.5%	113.7 mW/m^2	Liu et al. (2020a)
Beef extract wastewater	Continuous flow tubular MFC	COD: 1357 mg/L pH: 7.2 Temp: 20 °C	35.9%	0.99 W/m^2	Li et al. (2020)
Rice straw hydrolysate	Single-chamber air-cathode MFC	COD: 400 mg/L Temp: 30 ± 1 °C	72.0 ± 1.7%	137.6 ± 15.5 mW/m^2	Wang et al. (2014b)
Slaughterhouse wastewater	Dual chambered MFC	COD: 900 mg/L Temp 30 °C	93 ± 1%	578 mW/m^2	Katuri et al. (2012)
Vegetable based waste	Integrated MFC	COD: 0.93 kg COD/m^3-day pH: 7.0	80%	111.76 mW/m^2	Mohanakrishna et al. (2010)
Brewery wastewater	Novel trickling MFC	COD: ~4000 mg/L	57.5%	0.27 W/m^2	Gao et al. (2020)
Cheese wastewater	Microbial fuel cell	TCOD: 377 mg/L pH: 7.3 ± 0.2 Temp: ~21 °C	80%	3.2 ± 0.3 W/m^3	Kelly and He (2014)
White winery wastewater	Single chamber air cathode MFC	COD: 6400 mg/L pH: 6.9 Temp: 23 °C	95%	8.904 W/m^2	Sciarria et al. (2015)
Vegetable oil industry wastewater	Dual chambered MFC	pH: 5.7 Temp: 25 and 35 °C	80–90%	5839 mV	Firdous et al. (2018)
Brewery wastewater diluted in domestic wastewater	Single chambered MFC	COD: 1200 mg/L Temp: 35 °C	94%	174.0 mW/m^3	Larrosa-Guerrero et al. (2010)
Real dye wastewater	Single-chamber MFC	COD: 45,600 mg/L Temp: 25–26 °C	92–98%	123.2 ± 27.5 mW/m^3	Logroño et al. (2017)
Food processing wastewater	Two chamber MFC	COD: 1900 mg/L pH: 7.0	86%	230 mW/m^2	Mansoorian et al. (2013)
Petroleum refinery wastewater	Single chamber mediator-less MFC	COD: 1040 mg/L Temp: 29 ± 2 °C pH: 7.0	84.4 ± 0.8%	225 ± 1.4 mW/m^2	Srikanth et al. (2016b)
Palm oil mill effluent	Dual chamber MFC	COD: 60,600 mg/L Temp: 25–28 °C	45%	45 mW/m^2	Baranitharan et al. (2013)
Animal carcass wastewater	Up-flow tubular MFC	COD: 78.3 ± 10.5 g/L pH: 6.86 ± 0.13	50%	2.19 mW/m^3	Li et al. (2013)
Synthetic penicillin wastewater	Single-chamber air-cathode MFC	1 g glucose/L + 50 mg penicillin/L pH: 6.8–7.0 Temp: 24 ± 2 °C	90%	101.2 W/m^3	Wen et al. (2011)
Swine wastewater	Single chamber air cathode MFC	COD: 2735 ± 15 mg/L pH: 7.68 Temp: 30 °C	~80%	37.5 W/m^3	Ding et al. (2017)

membrane (Chang et al., 2023; Ferreira et al., 2017).

Reactor configuration plays a major role in electricity generation in MFC, and many studies have used membrane-less MFC and single-compartment MFC in continuous mode (Nguyen et al., 2021; Pandey et al., 2021) membrane in general, there are certain limitations in the single treatment process to remove the pollutants completely from industrial and domestic wastewater due to the complex composition. Consequently, novel set-ups or hybrid systems like MFCs were fabricated for the treatment of various wastewaters to generate electricity (Rathour et al., 2019). As mentioned, recent research has employed graphite-based truncated conical MFC (Nawaz et al., 2020), up-flow tubular MFC (Marassi et al., 2020), novel trickling MFC (Gao et al., 2020), MFC-anaerobic fluidized bed membrane bioreactor (Ren et al., 2014), and floating macrophyte-based ecosystem MFC (Mohan et al., 2011) in wastewater treatment. These MFC systems are easy to scale up for treating various wastewaters like beverage wastewater, dairy wastewater, chocolate wastewater, dye-containing wastewater, rice milling industry wastewater, palm oil mill effluents, molasses-based wastewater, pharmaceutical wastewater, sanitary wastes, and vegetable-based waste (Rathour et al., 2019; Raja et al., 2023).

From Table 4 and it could be deciphered that more than 80% of COD removal and a higher power output of 100 mW/m^2 were achieved (Mohanakrishna et al., 2010; Katuri et al., 2012; Mansoorian et al., 2013; Sciarria et al., 2015; Srikanth et al., 2016b; Ding et al., 2017; Córdova-Bautista et al., 2020; Liu et al., 2020a, 2020b). On the other hand, some research show lower COD removal efficiency with high power output (Gao et al., 2020; Wang et al., 2014b). It could be attributed to the initial substrate concentration, source of microorganisms, operating conditions, and reactor configurations of MFC. There has been limited study on the installation and long-term stability of MFCs for actual wastewater treatment facilities, consistent power generation, and running costs, even though improved COD removal efficiency and higher power output have been reported in various studies (Zhang et al., 2013).

5. Predominant microbes/biocatalysts for waste degradation in BESs

In the process of waste degradation, with the help of microbes, the chemical structure of the contaminant breaks down into water, carbon dioxide, and biomass sludge. For their survival, microbes consume nutrients and chemical compounds in waste. Almost all the chemical compounds, including hydrocarbons, could be degraded using different kinds of bacteria (Table 5). In BESs, *Geobacter sulfurreducens*, which is an iron-reducing bacteria (exoelectrogen), produces electrical current and highpower densities at optimal temperatures. High current generation could be achieved from common yeasts to extremophiles by providing optimum medium and survival conditions (Logan et al., 2019).

The electroactive bacteria (EAB) are called electrogens, electricegens, exoelectrogens, and *exo*-electrinogenic, which generate current. All these groups are associated with energy generation and energy conservation. The presence of electroactive bacteria has been identified

Table 5
List of biocatalysts used in a BESs for electricity generation.

Sl. No.	Microorganism	Substrate/co-substrate	Power density (mW/m^2)	References
1)	*Shewanella oneidensis* strain 14,063	Acid orange-7, Sodium pyruvate	>40	Fernando et al. (2012)
2)	*Rhodoferax ferrireducens*	Glucose, xylose sucrose, maltose, Fructose	158[a]	Liu et al. (2006)
3)	*Nocardiopsis* sp. KNU (S strain)	Cellulose	162	Hassan et al. (2012)
4)	*Klebsiella pneumoniae* strain L17	Glucose	34.8	Liu et al. (2009a))
5)	*Streptomyces enissocaesilis* KNU (K strains)	Cellulose	145	Hassan et al. (2012)
6)	*Pseudomonas* spp.	Wastewater	0.979	Daniel et al. (2009)
7)	Firmicutes	Glucose	40.3±3.9	Jung and Regan (2007)
8)	*G. sulfurreducens*	Acetate	48.4±0.3	Jung and Regan (2007)
9)	*Geobacter* spp.	Lactate	52±4.7	Jung and Regan (2007)
10)	*Proteobacteria* spp.	Ethanol	488 ± 12	Kim et al. (2007a)
11)	*Shewanella affinis* (KMM3586)	Cysteine	39	Logan et al. (2005)
12)	*Deltaproteo bacterium*	Marine sediment amended with acetate	-	Bond et al. (2002)
13)	*Saccharomyces cerevisiae* PTCC 5269	Glucose	283	Rahimnejad et al. (2011)
14)	*Saccharomyces cerevisiae*	Sugar mill wastewater	768	Siddique et al. (2018)
15)	*Scenedesmus quadricauda* (SDEC-8)	Domestic wastewater	62.93	Yang et al. (2018)
16)	*Chlorophyra, Nitrincola, Firmicutes*	Defined medium	31.92	Liu et al. (2020b)
17)	*Chlorella vulgaris*	Synthetic wastewater	16.72	Don and Babel (2021)
18)	*(Mixed culture) Corynebacterium variabile* SMS-14 *and Escherichia coli* SAM-14	Candy industry wastewater	19.45–353.65	Sambavi et al. (2020)
19)	Macrophyte plants	Domestic wastewater	24.104	Selvaraj and Velvizhi (2023)
20)	*Shewanella oneidensis MR-1 and klebsiella pneumonia* J2B	Glycerol	2.15	Kim et al. (2016)

[a] Current density (mA/m^2)

mostly in varieties of effluents, and sludges from effluent treatment plants (ETP). The electroactive microbes are majorly anaerobic or facultative anaerobic in nature. Exceptionally, some species can adjust to aerobic conditions. Based on their adjustability towards oxygen, *Geobacter* and *Shewanella* genus perform better as electroactive microbes. Single, pure bacteria cultures inferior in the current generation to the mixed culture strains. Diverse culture strains can easily break down the complex chemical compounds in the wastewater, and along with that, it has some merits, such as the non-requirement of sterilization, adaptability to the environment, the possibility to conduct continuous processes, and significant power production. The results of the researchers proved this statement by producing the current density of between 516 and 1300 mA/m^2 for mixed culture and 44 mA/m^2 for *Pseudomonas aeroginosa*, and 130 mA/m^2 for *Shewanella oneidensis*, respectively (Glaven, 2019; Li et al., 2019).

6. Kinetic models

The BESs is a complicated biological system that is made up of a variety of different physical, electrochemical, and biological processes. These processes interact with one another to produce a non-linear pattern in the performance of the system. Hence, finding the best conditions for improving system performance via experimental work would not be a cost-effective or time-efficient strategy. In this regard, mathematical models that consider microbial population dynamics, mass transfer in bulk liquid and biofilms, and electrochemical kinetics would be an alternate method for identifying influential variables and good estimation of the system's performance. Moreover, using these mathematical models, the operating conditions and configurations may be modified to better meet the system's final objective, which may be the extraction of energy, the treatment of wastewater, or both. This is possible without the need to conduct a large number of experiments. The great majority of models describe the system as a single-phase, focusing only on the anodic side and ignoring the cathodic reaction kinetics, which is one of the most influential factors affecting MFC performance (Ucar et al., 2017). Apart from that, in some simplified models, the BESs are considered as an ideally mixed system with anode-respiring bacteria in suspension in the bulk liquid phase (Picioreanu et al., 2010) or attached to electrode-forming biofilm with no substrate concentration gradient across the biofilm (Esfandyari et al., 2017a).

Esfandyari et al. (2017a) developed a dynamic model to predict several aspects including voltage and current generation from a batch mode dual chamber MFC fed with lactate and containing a pure culture of *Shewanella*, where it represents electron transfer by direct conduction. The Model studied MFC with 3 parts: bulk liquid in the anode chamber, biofilm attached to the anode electrode, and bulk liquid with oxygen as the acceptor in the cathode chamber. The parameters of the model were derived either from published literature or from the author's experiments. The specific growth rate of a microbe was analyzed using three kinetic models: Monod, Backman, and Tessier, and it was observed that the Monod model fit experimental results more accurately than the Backman and Tessier models. Using a Nernst-Monod model based on a conductive biofilm, the rate of substrate consumption was determined in this model. The electrochemical model was applied to account for ohmic, concentration, and activation overpotentials when estimating MFC performance (Esfandyari et al., 2017a). Later, this model was applied to a continuous system with a substrate volumetric flow rate of 3, 4.5, and 6 cm^3/h to predict aspects such as voltage and current productions, CO_2, and substrate concentrations in the bulk anode liquid. The empirical and predicted values were found to be in good agreement (Esfandyari et al., 2017b). However, this dynamic model was developed on the assumption that MFC is a lumped system, which is not the case, for example, as evidenced by the presence of concentration gradients in the biofilm. Due to substrate inhibition, a higher quantity of substrate in an MFC may cause its electrical performance to decline. Tessier, Haldane, and Aiba models were used to describe the behavior of dual chamber MFC on varying substrate concentrations of low to high amounts of glucose or date syrup employing *S. cerevisiae* as a biocatalyst (Jafary et al., 2013). In all three models, the growth term is substituted by electric output, such as voltage, current, or power, and the experimental data were used to determine the numerical values of the model parameters. The predictions of all three models were well-fitted to the experimental data (R^2 = 0.98–0.99) (Jafary et al., 2013). Cai et al. (2018) proposed a transient two-dimensional model for a single chamber air cathode MFC fueled with acetate and hosting two forms of microorganisms, exoelectrogens, and methanogens, in which electron transfer was assumed to occur through endogenous extracellular mediators. At varied biofilm porosities ranging from 0.5 to 0.9 and external resistances ranging from 10 Ω to 1000 Ω, the model evaluated the internal mass distribution and bioelectrochemical kinetics. Biofilm, biofilm-electrolyte interface, and anodic electrolyte are the model domains. The multiplicative Monod kinetics defines the growth rate of

exoelectrogens and the substrate consumption rate by exoelectrogens when mediators were involved in electron transfer, considering both the substrate concentration and oxidized mediator concentration. For the polarization curve and current generation, there was good agreement between simulated and experimental results. According to the simulated results for different biofilm porosities, higher porosities are better for reaching higher exoelectrogens concentrations and better distribution of exoelectrogens over the biofilm, as well as beneficial for acetate transfer through the biofilm and inhibiting methanogens growth. While simulations of varied external resistance showed that lower external resistance is preferable for exoelectrogens and getting increased mediator concentrations (Cai et al., 2018). The Butler–Volmer–Monod model which combines enzyme kinetics with electron transfer kinetics was developed to describe the polarization curve of the bioanode considering the electron transfer from microorganism to electrodes via redox component present inside the microorganism and has demonstrated a better match with the experimental data than predicted by using the Nernst–Monod model (Hamelers et al., 2011).

7. Artificial neural network (ANN) modeling

Artificial neural networks (ANNs) are regarded as a powerful modeling tool for complex non-linear systems, such as BESs, whose performance is highly sensitive to changes in the environment and whose parameters, such as biofilm thickness, electroactive microbes' activities, electron transfer mechanism, etc., are difficult to regulate or control. By training the neural network with relevant inputs that could impact the outputs, ANN could obviate the need for prior knowledge of the system's complex processes to model the system, resulting in a simplified and generalized model for the whole system. In the literature, the most prevalent ANN used for application of BESs is the feedforward multi-layer perceptron (MLP), using the Levenberg – Marquardt back-propagation algorithm, which consists of interconnected neurons organized in input, hidden, and output layers. Several studies have explored the application of ANNs in bioprocesses (Sewsynker-Sukai et al., 2017); nevertheless, the application of ANNs in BESs is a relatively new area of research. This will be helpful in determining the best operating conditions for achieving optimal performance of BESs, which will speed up the process of commercialization of these systems.

A multi-layer perceptron ANN trained by a backpropagation algorithm was developed to predict the current produced by MFC fed with wastewater such as beer brewery, sugar industry, dairy wastewater, municipal or paper industry as the output of the neural network. Inputs included were pH, BOD, COD, total suspended solids (TSS), and time (day) (Tardast et al., 2012). In another research, the bioelectricity generation from a specially designed membrane-less MFC that could potentially eliminate oxygen intrusion at the anode was evaluated, and the power output of this system was predicted using an ANN model. Temperature, pH, and electron acceptor concentration were selected as inputs for the network model, while power and current density were selected as outputs. The log sigmoid function was utilized as the transfer function, and three neurons in the hidden layer exhibited the highest R^2 values and were selected as the best among those evaluated (2, 4, and 5 neurons) (Tardast et al., 2014). A three-layer ANN model has been used to predict the power density-based performance of dairy wastewater-fed MFCs using time, liquid feed flow rate, and angle of anode inclination concerning flow direction as input variables (Jaeel et al., 2016). Experimentally, a maximum power density of 486 mW/m^2 at 40-Ohm external resistance was achieved when the anode was positioned perpendicular to the 1 ml/min feed direction. The authors developed the model employing a total of 96 experimental data, of which 60% were used for training, 20% for validation, and 20% for testing. This single-layer ANN was trained using the Levenberg–Marquardt back propagation (LMA) training algorithm, having a tangent sigmoid transfer function at the hidden layer and a purelin transfer function at the outer layer (Jaeel et al., 2016). The authors employed the same approach for predicting the power generation from cellulosic material, giant reed (GR), in MFC using an ANN model with time, particle size, and concentration of giant reed as inputs using a total of 170 experimental data obtained from MFC fed with domestic wastewater and GR. From a total of up to 16 neurons in the hidden layer, the least mean square error (MSE) was found for 12 neurons. In addition to the concentration of GR, the shape and size of the GR particles have been shown to have a significant effect on the power generation in the MFC, with powdered-type particles producing more power than fibrous-type particles (Ismail et al., 2017). Ali et al. (2018) applied a four-layer feed--forward ANN to predict the voltage produced by the MFC. The network structure was comprised of four input neurons, namely the concentration of the agar salt bridge, the temperature, the surface area of the electrode, and the total number of bacteria, as well as one neuron in the hidden layer and one neuron in the output layer, with the latter delivering the simulated voltage output. Using the constructed ANN model, the total count of bacteria was found to be the most significant independent variable in predicting changes in output voltage (Ali et al., 2018).

The performance of sugarcane effluent fed MFC inoculated with anaerobic sludge was predicted and validated using ANN in a recent research (Sreelekshmy et al., 2020). As input, the parameters that increase the activity of exoelectrogens were chosen, namely pH, biomass loading, % of Inoculum added, and electrical conductivity. Open circuit voltage, current density, and power density were the three outputs for the ANN. The optimal condition predicted by the ANN facilitated improved bacteria-electrode interaction, consequently lowering the internal resistance of MFC to 1.63×10^3 Ω and increasing the power density to 8314 mW/m^2. From the various topologies examined by varying the number of neurons in the hidden layer from 2 to 12, the least root mean square error was obtained with 10 neurons (Sreelekshmy et al., 2020). Approximating the polarization curve is a more accurate approach to modeling MFC performance using ANN as it also incorporates overshoot phenomena like voltage overshoots (Tsompanas et al., 2019). The authors developed an ANN with a topology of 4–10-1 neurons that were trained using data from experiments involving two distinct membrane materials and two distinct electrode configurations in cylindrical-type MFC fed with human urine. In contrast to prior ANN research on MFC, load resistance was used as an input parameter in this study. In another study, the effect of human urine flow rates on the performance of ceramic MFC was simulated using ANN (de Ramón--Fernández et al., 2020). By training the network using second-order algorithms, the Quasi Newton, Levenberg Marquardt (LM), and Conjugate Gradient, three MLPs were developed and evaluated in terms of prediction accuracy and convergence time. The LM algorithm was the most accurate ($R = 95\%$) and had the fastest convergence time (7.8 S) of all the tested algorithms. The network was trained using a total of 288 test experiments conducted at sixteen distinct flow rates.

Similarly to MFC, an ANN model was developed to predict the hydrogen yield from MEC. Using a committee of ANNs, Sewsynker et al. (2015) approximated the performance of MEC based on the 50 data points available from 15 previously published papers. The ANN was developed containing six neurons in the input layer, six, eight, eleven, twelve, or fourteen neurons in the hidden layer, and one neuron (H_2 production) in the output layer. The input variables were substrate type, substrate concentration, pH, temperature, applied voltage, and MEC configuration. The most influential factor on MEC performance, as determined by the developed committee ANN, was found to be the substrate type used.

An artificial neural network was used for generating a bioclimatic model for predicting the microbial community structure by incorporating the environmental parameters and the microbial interactions (Larsen et al., 2012). To predict the performance of MFC, a Bayesian interaction network-based ANN was developed (Lesnik and Liu, 2017). This model first predicts the structure of the microbial community in the biofilm based on wastewater characteristics. The predicted biofilm

community and input wastewater characteristics were then used to predict the system performance, including power density, Coulombic efficiency, and COD removal rate, which were predicted with an error of 16.01 ± 4.35, 1.77 ± 0.57, and 4.07 ± 1.06%, respectively, in that study by the authors.

Table 6 displays the various input and output parameters chosen by different authors, the most optimum ANN topology, the optimization algorithm used, the error values observed between the experimental and predicted values, and the best validation performance. It is noteworthy to mention that, the functional stability of BESs in terms of its resistance and resilience to environmental perturbation, such as pH fluctuation during operation can predict using machine learning models by incorporating microbial community structure and environmental disturbance data (Lesnik et al., 2019). By incorporating a large data set, such as omics data obtained under a variety of operational disturbances, a more accurate date for predicting the performance of engineered systems like MFC can be developed.

8. Opportunity and future perspectives

The microbial fuel cell is a technology that can produce energy from the action of microorganisms. BESs are very cheap, fast, simple, and also rectify the current electricity needs. This technology has been widely used in the past few years. However, it is very important to consider the production of low current density in microbial fuel cell operation. The existing design parameter for the optimization of the reduction of losses is affected by ohmic, activation, and concentration overpotentials (Nastro, 2014; Logan et al., 2018). Furthermore, reduction in power is also caused by some of the redundant reactions, for example, due to direct oxidation of fuel by oxygen diffusion into the microbial metabolic reactions or anodic chamber. It does not improve the process, so it must also be treated.

Electrogenic microorganisms play a crucial role in determining the performance of BESs. These microorganisms have the unique ability to transfer electrons produced by their metabolic processes to external electrodes, thereby facilitating the production of electrical current. To improve the process of BESs, it is necessary to improve the performance of electricigens (Verma et al., 2021). The development of synthetic biology and metabolic engineering leads to the modification of creating novel electricigens or modifying current electricigens and improving their electrochemical activities (Uma Vanitha et al., 2017). The improvement in power density in the MFC system is not only determined by the electricigens but also enhanced by the electrode spacing, architecture, and electrolyte conductivity of the MFC (Hindatu et al., 2017). The enhancement in these parameters would also enhance the efficiency of power generation in MFC. Furthermore, MFC has been incorporated with a combination of many processes to make this method economically feasible.

The wastewater can be utilized in the MFC system, hence, it could be an attractive substitute to reduce the cost of the MFC system and also an effective way for the management of wastewater. The valuable product that comes from MFC is the generation of H_2. Hydrogen can be generated in the cathode, due to the migration of protons to cathode. Bioremediation by MFC is an advanced promising technology. MFCs have been anticipated for the clean-up of various types of contamination, such as aromatics, substituted organic compounds, and heavy metals, etc. (Rosenbaum and Franks, 2014). During this bioremediation process by MFC, electricity is generated and making the process cost-efficient. The amalgamation of MFC technology with other applications can explore the possibility of applying MFCs as a sustainable technology for the treatment of wastewater and also for the generation of energy.

9. Conclusions

BESs are advanced treatment techniques that have been extensively studied in the lab and have demonstrated their reliability in producing energy using the inherent features of a biocatalyst. In this review, the performance of various biocatalysts utilized in BESs for electricity generation has been summarized, along with the process/environmental conditions used/tested by researchers who treated various types of wastewaters. In various systems, low current density/yields have been noticed; nevertheless, at optimal operating conditions and by activating the enzyme and cell activity, different types of substrates/wastewaters have been treated successfully to generate power. The enzyme and electron transfer kinetic models have been developed to describe the polarization curve of the bioanode when the electron transfer occurs from the microorganism to the electrodes via a redox component. The deployment of artificial neural network models has been shown to be dependable, particularly in establishing the best conditions for improving the performance of reactors. From a practical viewpoint, this

Table 6
Literature reports on the different artificial neural network topologies and conditions used to predict the performance of BESs.

Input parameters	Output parameters	ANN topology	Optimization algorithm	R^2 value	Mean square error	Best validation performance and the epoch size	References
Time (days), flowrate (mL/min), angle (anode inclination with respect to the flow direction)	power generation (mW/m^2)	3:16:1	Levenberg – Marquardt back propagation (LMA)	0.99889	6.4203	41.1857 at epoch 117	Jaeel et al. (2016)
Time duration (days), concentration of PGR in the wastewater (g/L), and particle size of the PGR (mm)	Power generation (mW/m^2)	3:16:1	Levenberg – Marquardt back propagation (LMA)	0.9993	6.0616	78.3309 at epoch 38	Ismail et al. (2017)
Logarithmic value of load resistance, cylinder material, electrode location and cathode electrode size	Voltage	4:10:1	Levenberg – Marquardt back propagation (LMA)	0.99662	NR	NR	Tsompanas et al. (2019)
Feed flow (mL/min), membrane porosity (%), bulk resistance (Ω)	Output power (μW/cm^2)	3:8:1	Levenberg – Marquardt back propagation (LMA)	0.9528	7.9	5.8637 at epoch 7	de Ramón-Fernández et al. (2020)
		3:9:1	Quasi - Newton	0.93236	7.89	6.3643 at epoch 11	
		3:11:1	Conjugate gradient	0.92057	10.07	8.2356 at epoch 19	
pH, inoculum loading (%), biomass loading (%), and electrical conductivity (mS/cm)	Output circuit voltage (mV), current density (mA/cm^2) and power density (mW/cm^2)	3:10:1	Levenberg – Marquardt	0.9616	>40 (RMSE)	1170.8423 at epoch 8	Sreelekshmy et al. (2020)
Temperature, pH, and electron acceptor concentration	Current density (mA/m^2) and power density (mW/m^2)	3:3:1	Levenberg – Marquardt	0.98868	2.387×10^{-3}	NR	Tardast et al. (2014)

treatment technology would enable the recovery of energy from many types of waste (e.g., liquid and solid matrices) while avoiding excess sludge generation.

CRediT authorship contribution statement

P. Mullai: Conceptualization, Visualization, Writing – review & editing, Supervision. **S. Vishali:** Conceptualization, Visualization, Writing – review & editing, Supervision. **S.M. Sambavi:** Conceptualization, Writing – review & editing. **K. Dharmalingam:** Conceptualization, Visualization, Writing – review & editing, Supervision. **M.K. Yogeswari:** Conceptualization, Writing – review & editing. **V.C. Vadivel Raja:** Conceptualization, Writing – review & editing. **B. Bharathiraja:** Conceptualization, Writing – review & editing. **Bayar Büşra:** Conceptualization, Visualization, Writing – review & editing. **Haris Nalakath Abubackar:** Conceptualization, Visualization, Writing – review & editing. **Md Abdullah Al Noman:** Conceptualization, Visualization, Writing – review & editing. **Eldon R. Rene:** Conceptualization, Visualization, Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in the paper.

Data availability

No data was used for the research described in the article.

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ORIGINAL PAPER

Sustainable synthesis of automobile fuel additive from glycerol and acetone and catalyst reusability studies

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Abstract

The present study examined the production of Solketal, a gasoline additive, using glycerol and acetone. For the ketalization experiments, a potential cation exchange resin Ceralite IR-120 was utilized. The effect of agitation speed, temperature, catalyst dosage, and feed composition on the rate of glycerol conversion was studied. For a molar ratio of 1:16 between glycerol and acetone, the experimental results indicated a conversion rate greater than 90%. The experimental studies indicate low mass transfer resistances. The activation energy for the chemical reaction was calculated to be 54.34 kJ/mol, indicating that kinetics rather than thermodynamics dominates this process. A pseudo-homogeneous reaction model that characterizes the acetalization process over the catalyst also concurred with the experimentally determined conversion rate. Catalyst reusability studies showed catalytic activity for up to six recycles.

Keywords Heterogeneous catalyst · Biodiesel · Glycerol · Acetone · Solketal · Acetalization · Reusability

Introduction

Increasing greenhouse gas emissions in the atmosphere has become a major concern throughout the world, and hence, reduction in fossil fuel usage has become very important. At this juncture, biofuels and gasoline additives have received a great deal of attention due to their ability to cut down emissions (Alalwan et al. 2019; Okolie et al. 2022). Biomass is a renewable resource and may be used to produce bioenergy/biofuels without increasing greenhouse gas emissions (Thornley et al. 2015). Biofuels are great alternatives to fossil fuels. Fischer–Tropsch synthesis produces a wide range of biofuels, including bio-methanol, bioethanol, biodiesel, and synthetic diesel, from biomass (Ahorsu et al. 2018; Manikandan et al. 2022). Current international interest in biodiesel is due to several advantages over petroleum diesel. Biodiesel is a non-toxic and biodegradable alternative and can be used in conventional diesel engines without any modifications (Riaz et al. 2022; Aljaafari et al. 2022). Its superiority over petroleum-based diesel reflects better lubricity, lack of sulfur, and aromatics, along with reduced carbon emissions (Singh et al. 2018). Hence, it garnered great attention in the recent past. It is usually produced along with glycerol, which is a by-product, via the transesterification of triglycerides in vegetable oils/animal fats while using alcohol in an acid or alkali catalyst. Glycerol/glycerine is also called 1, 2, 3-propanetriol and is generated almost 10% (by volume) during the production of biodiesel (Rezania et al. 2019). With the increasing production of biofuels (biodiesel and bioethanol) throughout the world, the simultaneous production of large amounts of glycerol has also seen a large spike, and it is expected to reach 4 million tons by 2027 (Bhatt et al. 2018). Large-scale manufacturers can easily refine the glycerol economically but for small-scale manufacturers, it is always challenging with refining costs, and on top, they must pay to get rid of glycerol from their plants. Thus, the price of glycerol is expected to come down

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quite rapidly as the production of biodiesel keeps increasing. Therefore, it is worthwhile to consider the efficacy of glycerol in producing value-added products on an industrial scale to enhance the sustainability of the biodiesel industry (Ayoub and Abdullah 2012; De Corato et al. 2018; Gutiérrez Ortiz 2020).

Early research on glycerol showed the possibility of production of 1,3-propanediol through hydrogenolysis (Wang et al. 2020), glycolic acid dihydroxyacetone and glyceraldehyde via oxidation (Zhang et al. 2012), and form acrolein by dehydration processes (Sung and Cheng 2017), which, in turn, can result in acrylic acid upon oxidation, and then, polyglycerol and polyglycerol esters when polymerized. However, glycerol is unsuitable for fuel applications to the hydroxyl groups but is an excellent source for making oxygenated compounds, e.g., acetals and ketals, which can be used as additives in the fuels for the reduction of carbon emissions. On top, glycerol-based acetals are used as surfactants, disinfectants, and flavors (Kaur et al. 2020; Checa et al. 2020). The reaction between glycerol and acetone leads to the formation of two oxygenated compounds: 2,2-dimethyl-1,3-dioxane-5-ol and 2,2-dimethyl-1,3-dioxolane-4-methanol, with branching, as illustrated in the scheme employed for the acetalization of glycerol. Among these, Solketal is a good fuel and helps improve the flow properties of liquid fuels at low temperatures in the transportation sector. Also, it helps improve the oxidation stability and octane number of gasoline while reducing gum formation (Ilgen et al. 2016; Corrêa et al. 2021). It is also used as a solvent in the polymer industry for plasticizing polymers. It is used in pharmaceutical preparations also as solubilizing and suspending agent (Vannucci et al. 2021) (Fig. 1).

Various catalysts were used for the conversion of glycerol to Solketal. These catalysts include iron complex, Purolite, Amberlyst-35, Indion, nitric acid-modified montmorillonite clay, heteropolyacids (HPAs), and many more (Corrêa et al. 2021). In general, the acetalization of glycerol is done using homogeneous acid catalysts, such as mineral acids (H_2SO_4, HF, and HCl) and p-toluene sulfonic acid (Poly et al. 2019). Esposito et al. (2017) and Da Silva et al. (2020) used iron-based homogeneous catalyst with glycerol-to-acetone molar ratio ranging between 1:4 and 1:20. In both cases, the conversion and selectivity were reported to be more than 95%. However, the catalyst was reported to lose its activity after four recycles. However, this approach suffers from corrosion of process equipment along with difficulty in separating the catalyst from the product stream. In addition, it also has environmental concerns regarding effluent disposal. Nevertheless, these challenges can be overcome while using heterogeneous catalysts. Zeolites used as catalysts by various researchers showed selectivity of 85% for glycerol acetone molar ratio ranging between 1:2 and 1:10. However, the catalyst showed very little or no reusability (Manjunathan et al. 2015; Kowalska-Kus et al. 2017). Different studies were reported on the acetalization of glycerol using solid acid catalysts such as Amberlyst-36, Amberlyst-15, montmorillonite K-10, niobic acid, HZSM-5, HUSY, amorphous and mesoporous silica, sulfated zirconia, and zeolites such as H-BEA, H-MOR, H-MFI, and H-FER (Gonçalves et al. 2008; Testa et al. 2013; Rossa et al. 2019). Ion-exchange type catalyst consisting of Indion 225 Na led glycerol conversion of 35% (Sulistyo et al. 2020), and Amberlyst-35 showed conversion of 70% (Moreira et al. 2019). Deutsch et al. (2007) investigated the activity of various heterogeneous catalysts for the generation of cyclic acetals via glycerol condensation reaction with aldehydes. A high molar ratio of acetone to glycerol (6:1) resulted in a high yield of more than 90% of Solketal with high selectivity in a batch reactor (Vicente et al. 2010). Although different researchers showed the potential conversion of glycerol into fuel additives or value-added products through the acetalization process, none of them had reported any detailed kinetic studies with acetone over the solid acid catalysts (Deutsch et al. 2007; Vicente et al. 2010; Smirnov et al. 2018; Zahid et al. 2020). Other catalysts, including clays, metal oxides, and ionic liquids, showed good catalytic conversion but very poor recyclability. The literature reported that the global market of Solketal is expected to account for around $108.4 billion by 2028 (Ao and Rokhum 2022).

This information is very critical from the practical implementation point of view for the utilization of glycerol in producing value-added fuel additives. Therefore, considering

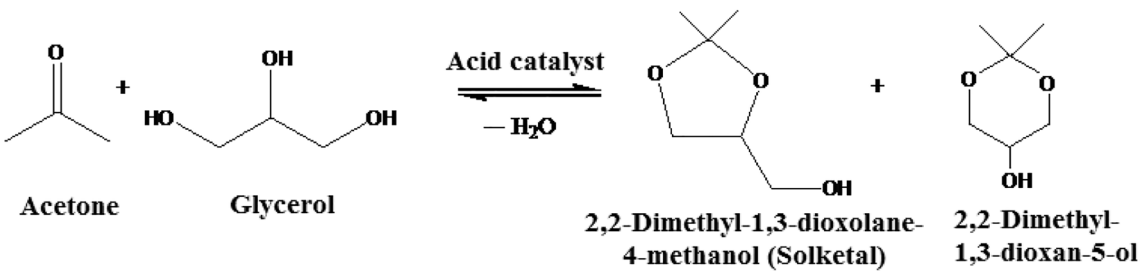

Fig. 1 The scheme used in the acetalization of glycerol with acetone

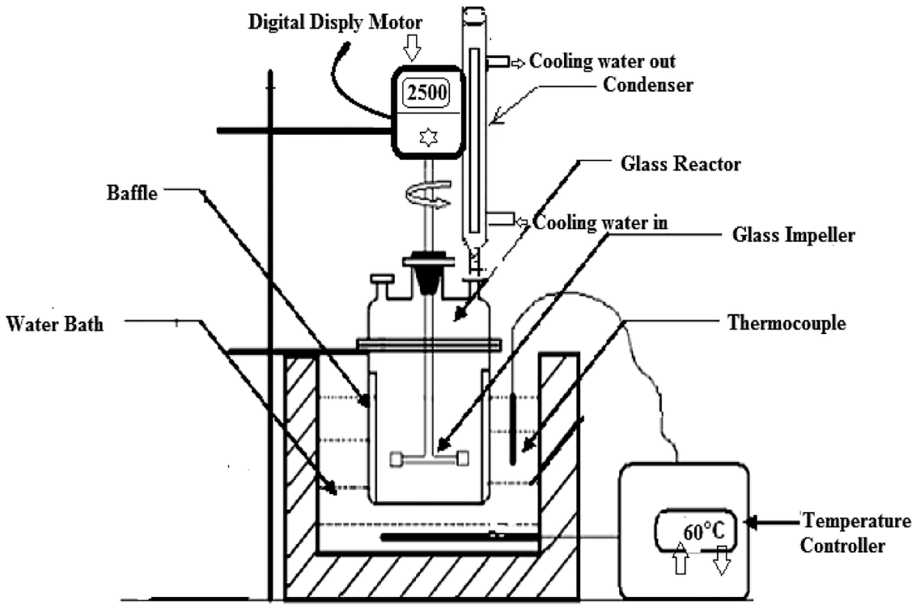

Fig. 2 A schematic diagram for the batch reactor assembly

the great importance of the above in the long term, here, we have done detailed kinetic studies of the acetalization of glycerol with acetone. The primary objective of this work was to explore the kinetics of the acetalization reaction of glycerol with acetone in a batch mode over a solid acid catalyst, Ceralite IR-120. We have studied the effect of various parameters to shed light on the practical viability of the adapted approach. The outcome of these studies could easily help propose a suitable reaction mechanism and a rate equation with the kinetic parameters measured experimentally.

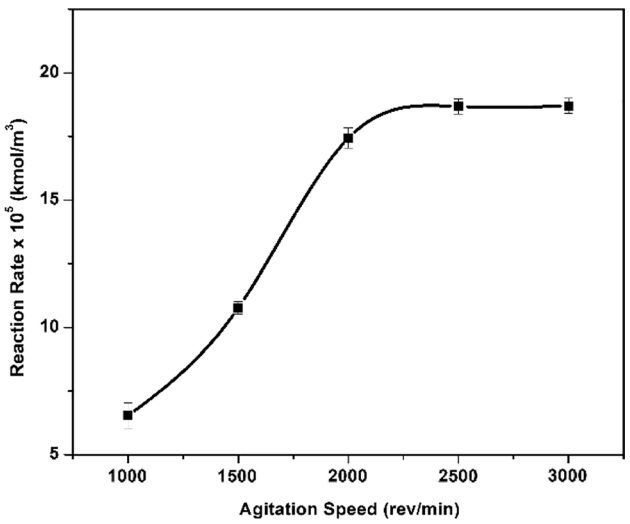

Fig. 3 Effect of agitation speed on reaction rate [Conditions: temperature = 303 K; feed mole ratio (glycerol:acetone) = 1:10; catalyst loading = 10% (W/V); and matching glycerol conversion = 5.0%]

Experimental methods

Materials

Both glycerol and acetone (>99.5 wt. % purity) were procured from Merck Specialty Pvt. Ltd. Commercial grade N, N-dimethyl formamide (DMF) (>99.5 wt. % purity) was obtained from SD Fine Chem Pvt. Ltd., Mumbai, India. Solketal (1, 2-Isopropylideneglycerol, 99 wt. %) was purchased from Sigma-Aldrich, India, as a calibration standard for gas chromatography (GC) analysis. The strong cation exchange resin, Ceralite IR-120 (20–50 mesh, ionic form H^+ with ion-exchange capacity min. 4.5 meq/g) (equivalent to Amberlite IR-120) from Central Drug House (P) Ltd., was used as the catalyst.

Experimental procedure

The glycerol acetalization reactions were performed in a 20 cm^3 fully baffled three-necked glass reactor equipped with a glass turbine impeller connected to a high-speed motor and a vertical condenser. The reactor's temperature was controlled precisely with an accuracy of ± 0.03 K using an external thermostat containing an external thermocouple inserted inside the reaction mixture, and a schematic for the setup used in our experiments is shown in Fig. 2.

The acetalization experiments were conducted using a predetermined amount of reactant mixture comprising glycerol and acetone, taken in a standard volumetric flask, following the required mole ratios, and then diluted with DMF solvent to achieve a total volume of 100 cm^3. The resulting mixture was then introduced into the reactor and maintained at a constant temperature using a water bath.

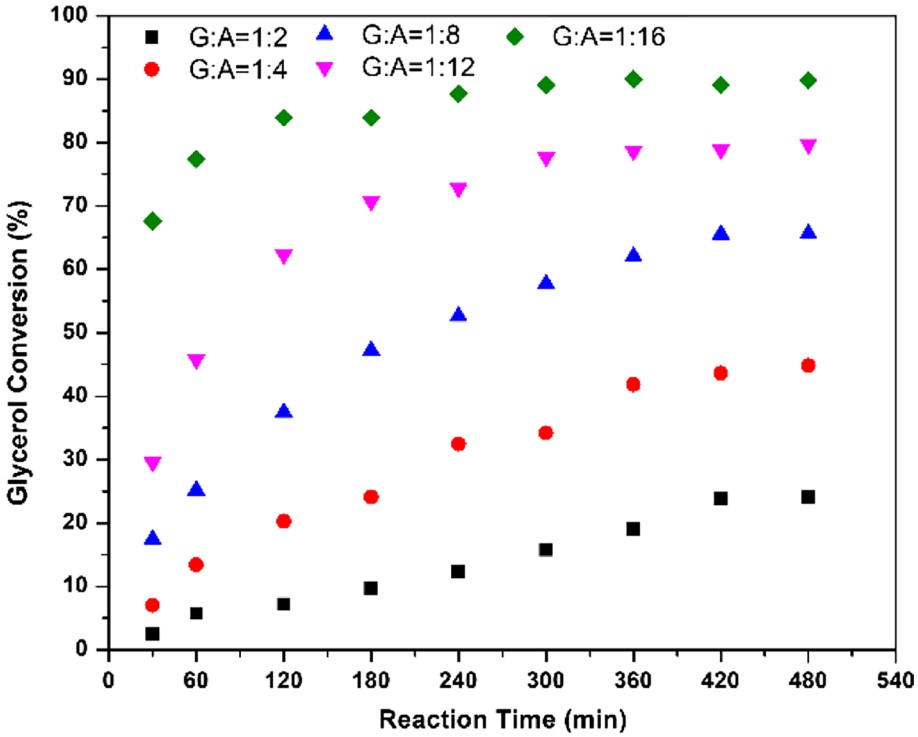

Fig. 4 Effect of feed mole ratio on glycerol conversion [Conditions: temperature = 298 K; the speed of agitation = 2500 rev/min; and catalyst loading = 10% (W/V)]

Once the temperature was set, the catalyst solution was added to the reactor simultaneously. To improve the solubility of glycerol in acetone, DMF was used as a suitable solvent, leading to the formation of a single phase, indicating proper homogenization. Liquid samples of approximately 0.2 ml were extracted at regular intervals once the two phases (liquid and solid) separated clearly without agitation. The samples were then stored in an ice bath until analysis through gas chromatography (GC 8610). The samples from the organic phase were collected at various time intervals and analyzed in a gas chromatograph (GC) (Thermo Scientific Trace 800 Model) equipped with a capillary column measuring 30 m in length, 0.25 mm in inner diameter, and a 0.25-µm film with 5% phenyl methyl polysiloxane as a stationary phase. Nitrogen was employed as the carrier gas, and the GC used a flame ionization detector. The composition of the samples was analyzed by comparing peak areas against a pre-calibrated curve, and the actual glycerol conversions and the moles of products were measured from the calibration file prepared in GC using various standards made from pure compounds.

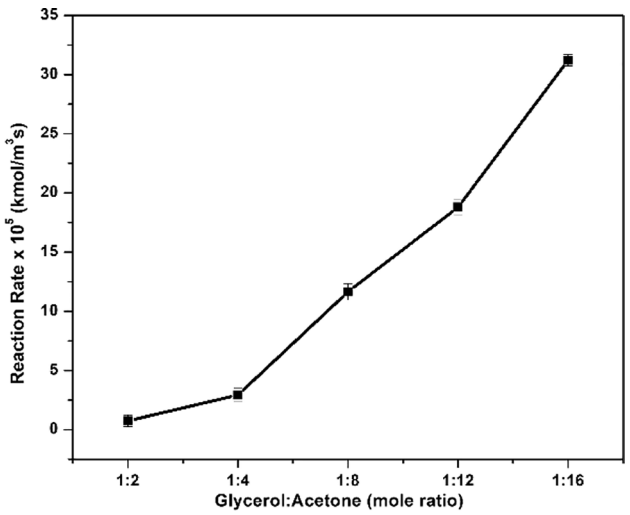

Fig. 5 Effect of feed mole ratio on reaction rate [Conditions: temperature = 298 K; the speed of agitation = 2500 rev/min; catalyst loading = 10% (W/V); and matching glycerol conversion = 5.0%]

Results and discussion

Effect of agitation speed

Initially, the effect of agitation speed was examined to determine the role of mass transfer resistances on the reaction system, as it is very important before performing the kinetic studies of any reaction. The experiments were conducted at various agitation (stirring) speeds in the range of 1000–3000 rev/min under otherwise identical experimental conditions to investigate the effect of mass transfer on the reaction's kinetics. The reaction rates at matching 5% glycerol conversion were compared in this stirring speed range, and it was observed to increase with the increase in speed up to 2000 rev/min, as shown in Fig. 3. Above 2000 rev/min, the effect of speed on reaction rate is negligible, and it could be concluded that the mass transfer effect is unimportant at speeds above 2000 rev/min. Therefore, all other experiments were

Table 1 Effect of reaction temperature on conversion at different temperatures [Conditions: feed mole ratio (glycerol:acetone) = 1:6; catalyst loading = 5% (w/V); and the speed of agitation = 2500 rpm]

Time (min)	Conversion of glycerol (%)						
	Reaction temperature (K)						
	303	308	313	318	323	328	333
5	2.8	3.4	5.9	8.7	10.6	14.0	17.2
10	4.3	7.1	10.2	12.9	16.2	22.2	29.0
15	6.0	9.5	14.5	17.8	23.0	27.5	34.8
30	10.8	17.5	21.9	27.1	33.0	40.4	48.0
45	15.3	22.8	27.6	35.9	41.0	48.7	54.2
60	20.0	30.4	33.5	40.3	46.9	54.4	58.7
120	31.5	43.4	46.5	54.6	60.5	63.9	65.4
240	47.2	52.4	60.7	62.7	66.5	70.4	66.7
360	56.7	60.5	66.0	68.9	69.9	71.4	67.3
480	61.4	65.7	69.4	71.9	73.6	71.4	67.3
Equilibrium conversion	93.3	87.4	84.1	78.2	74.8	71.4	67.3

conducted at a constant 2500 rev/min speed to eliminate the mass transfer effects, and the reactions were kinetically controlled. In this study, the reactants could quickly diffuse into the pores without any significant resistance in a macroscopic ion-exchange resin used as a catalyst. Hence, internal mass transfer resistance was expected to be negligible.

Effect of initial composition of reaction mixture

Experiments are carried out to analyze the influence of the initial molar concentration of reactants on conversion and the reaction rate at 298 K with 10% (W/V) loading of the catalyst and at a constant stirring speed of 2500 rev/min while varying the initial acetone-to-glycerol molar ratio from 2 to 16. Increasing the acetone-to-glycerol molar ratio increased glycerol conversion, as shown in Fig. 4. The rates of reaction of glycerol were calculated at a 5% conversion level for various feed compositions. From Fig. 5, it can be observed that the rate of reaction of glycerol increases with an increase in the concentration of acetone in the reaction mixture. Therefore, the reactants' initial mole ratio strongly affects the reaction kinetics: A higher mole ratio results in a higher reaction rate and more extensive conversion. The experimental outcomes demonstrate that the excess of acetone in the composition leads to enhancing the reaction in the forward direction thermodynamically to escalate the glycerol conversion. Increased reactant concentrations would result in a greater reaction rate, thereby tending to further product yield.

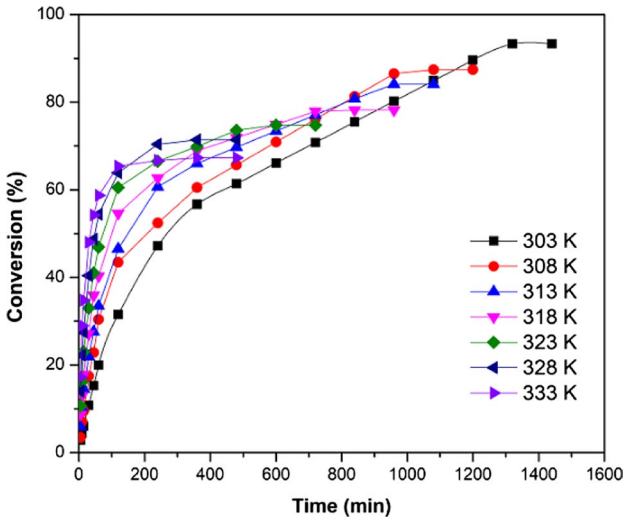

Fig. 6 Effect of temperature on conversion [Conditions: feed mole ratio (glycerol:acetone) = 1:6; the speed of agitation = 2500 rev/min; catalyst loading = 10% (W/V); and matching glycerol conversion = 5.0%]

Effect of temperature

The effect of reaction temperature on the acetalization reaction of glycerol was explored at different temperatures ranging from 303 to 333 K with the fixed conditions of acetone/glycerol mole ratio of 6 and catalyst loading of 5% (W/V), and the variation of glycerol conversion with temperature is shown in Table 1 and Fig. 6. Based on the equilibrium conversion data obtained, higher temperatures reduce the equilibrium product yield, consistent with thermodynamic studies showing exothermic behavior. Furthermore, the initial rate of the ketalization process increases with increasing temperature, similar to that shown in the literature (Nanda et al. 2014). From the conversion values, it was inferred that high conversions were achieved at low temperatures due to exothermic reaction; however, this was compensated with longer reaction times (Moreira et al. 2019). The reaction rate was also calculated at a matching glycerol conversion of 5%, as shown in Fig. 7. The Arrhenius plot of logarithmic initial rates (calculated from the best polynomial fit curve with conversion–time data) versus the inverse reaction temperature

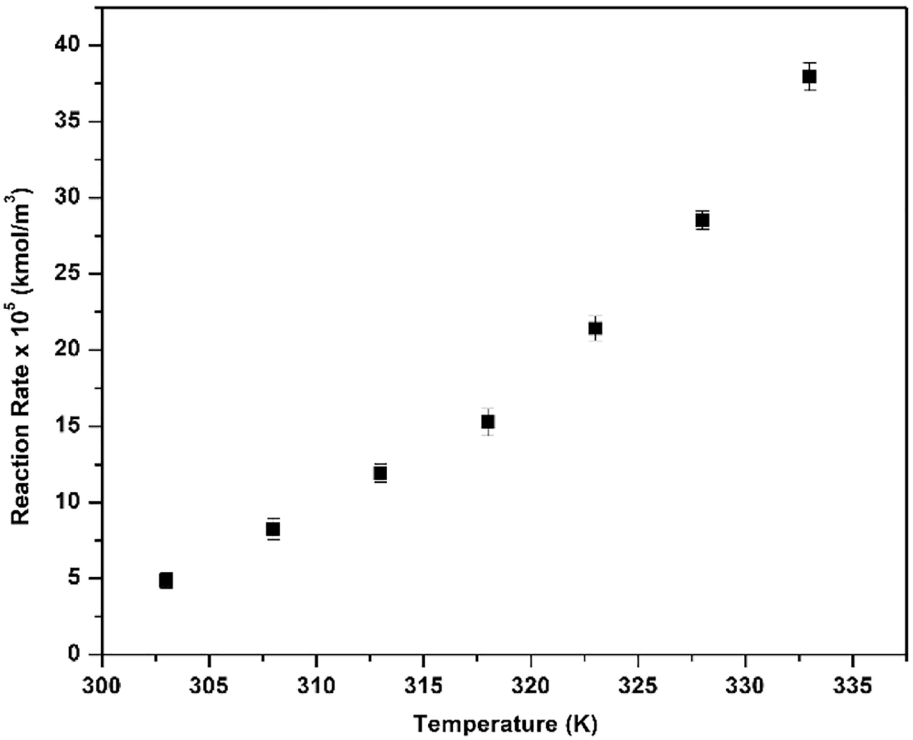

Fig. 7 Effect of temperature on reaction rate [Conditions: feed mole ratio (glycerol:acetone) = 1:6; the speed of agitation = 2500 rev/min; catalyst loading = 10% (W/V); and matching glycerol conversion = 5.0%]

was made, as shown in Fig. 8. The slope of the best-fit line determined the apparent activation energy as 54.34 kJ/mol.

The equilibrium constant values at different temperatures were calculated based on the equations considered from the literature (Nanda et al. 2014) and are shown in Table 2. The equilibrium values were evaluated by keeping the reaction times very long until two consecutive values were similar. From Table 2, it was inferred that high conversions were achieved at low temperatures due to exothermic reaction (Moreira et al. 2019); however, this was compensated with longer reaction times.

The equilibrium constant is calculated using the following formula:

$$K_c = \frac{[\text{solketal}]*[\text{water}]}{[\text{acetone}]*[\text{glycerol}]}$$

A graph plotted between the $ln\, K_c$ vs $1/T$ showed a linear correlation. This plot is used to calculate the thermodynamic properties such as enthalpy and entropy which is given by the expression:

$$\ln K_c = \frac{\Delta S^o}{R} - \frac{\Delta H^o}{R}\frac{1}{T}$$

where ΔH^o and ΔS^o are the standard enthalpy and entropy at 298 K (kJ/mol K). The linear fitting of the experimental data obtained the following equation:

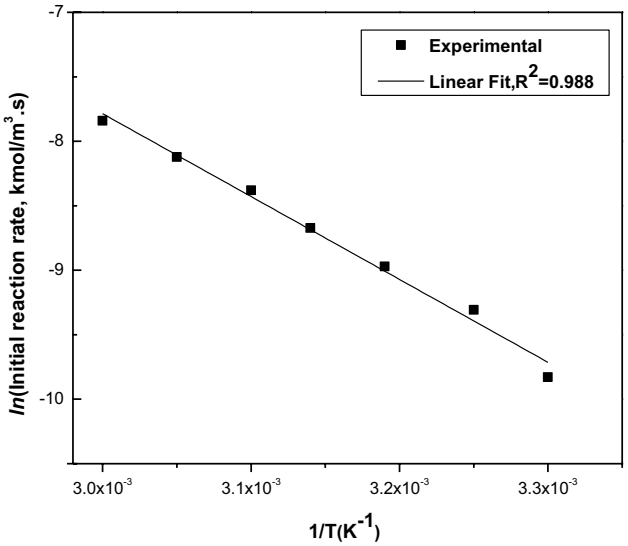

Fig. 8 Arrhenius plot of ln (initial rates) versus 1/T [Conditions: temperature = 303 K; feed mole ratio (glycerol:acetone) = 1:10; the speed of agitation = 2500 rev/min; and matching glycerol conversion = 5.0%]

Table 2 Equilibrium conversion (X_E) and equilibrium constant (K_c) values evaluated with respect to temperature

Temperature (K)	Equilibrium conversion, X_E	Equilibrium constant, Kc
303	93.3	1.56
308	87.4	0.89
313	84.1	0.72
318	78.2	0.51
323	74.8	0.39
328	71.4	0.34
333	67.3	0.26

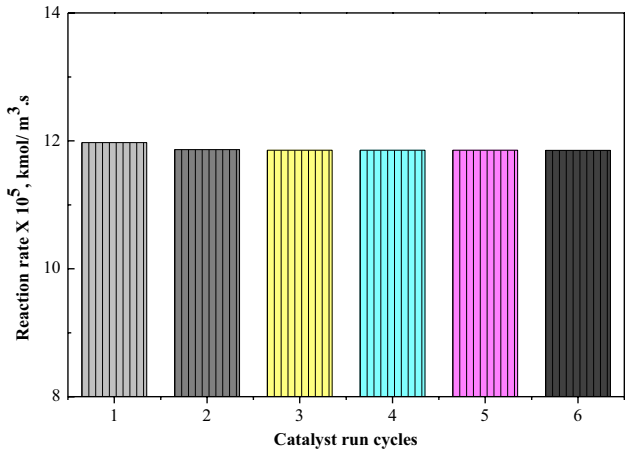

Fig. 9 Variation of reaction rate with reuse time [Conditions: reaction temperature = 313 K; feed mole ratio (glycerol:acetone) = 1:6; the speed of agitation = 2500 rev/min; catalyst loading = 5% (W/V); and matching glycerol conversion = 5.0%]

$$\ln K_c = 5729.1\frac{1}{T} - 18.613$$

Comparing the above two equations, we get $\Delta H^o = -154.67$ kJ/mol K and $\Delta S^o = -47.61$ kJ/mol K. The negative values suggest that the reaction is exothermic, similar to that reported in the literature (Ribeiro et al. 2022).

Recycling (reusability) of the catalyst

The catalyst was reused for five additional cycles to evaluate the stability of the ion-exchange resin in the glycerol and acetone reaction. Each cycle was conducted at 313 K with a glycerol-to-acetone molar ratio of 1:6 and a reaction time of up to 8 h. Following an 8-h reaction time, the catalyst was recovered through filtration, thoroughly washed with distilled water to remove any entrapped glycerol, acetone, Solketal, and solvent, and then air-dried overnight at 308 K. The dried catalyst was subsequently reloaded into the reactor. The glycerol conversions for each reaction cycle were very similar, and no significant catalyst deactivation was observed in the analyses conducted (Fig. 9).

Kinetic studies

The acetalization of glycerol with acetone was performed in the presence of a solid acid catalyst. Solketal was identified as the only product of the cation exchange resin-catalyzed acetalization reaction. From the conversion versus time data at diverse temperatures, plots of – ln(1-X_G) (where X_G is conversion of glycerol) versus reaction time were made, and the plots were observed to be well fitted with linear relation having origin as slope, as shown in Fig. 10. The pseudo-first-order rate constants are obtained from the slopes of straight lines at different reaction temperatures in the selected range. The results show as the temperature increased from 303 to 333 K for the glycerol-to-acetone molar ratio of 1:6 and catalyst loading of 5% (w/V), the apparent rate constant increased from 7.18×10^5 to 51.35×10^5 s^{-1}. The plot (Fig. 10) shows a less than linear fit for temperature

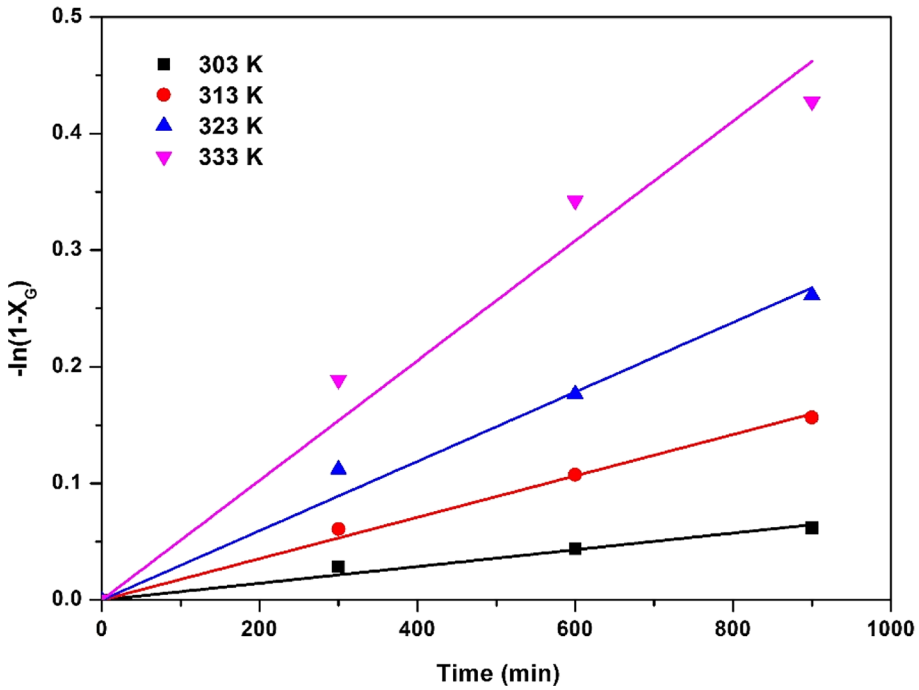

Fig. 10 The plot of the pseudo-homogenous first-order integrated kinetic model

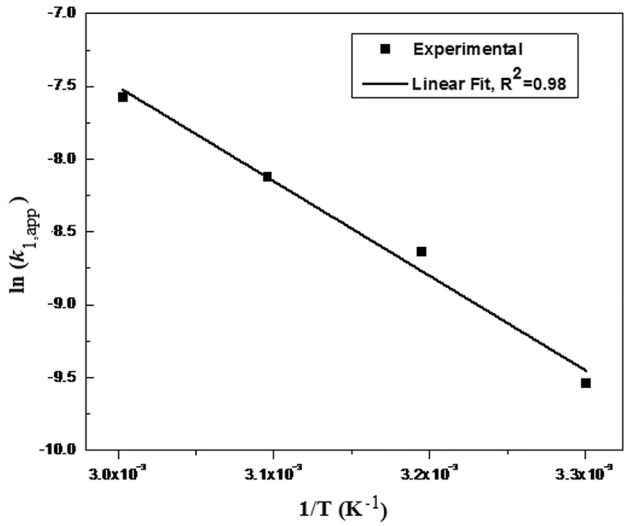

Fig. 11 Arrhenius plot of ln ($k_{1,app}$) versus 1/T

333 K. This is attributed to the fact that as the temperature increases, the reaction rate increases, making the curve non-linear, as reported by Moreira et al. (2019). However, we have considered a linear pseudo-first-order reaction to measure the apparent rate constant used to evaluate the activation energy at all the temperatures.

In a graph plotted between the logarithmic values of the apparent rate constant and the inverse of reaction temperature, a reasonably good straight-line fit was observed and is shown in Fig. 11. The apparent activation energy and the frequency factor are calculated from the slope and intercept as 54.88 kJ/mol and 13.05×10^4 s^{-1}, respectively.

Conclusions

Glycerol, a by-product of the biodiesel industry, was converted into a valuable product, Solketal, ketalization with acetone, another low-cost by-product of the cumene process phenol. A heterogeneous catalysis approach was employed to synthesize Solketal using an acidic ion-exchange resin (Ceralite IR-120) as a solid acid catalyst. The reaction mixture's intense agitation was kinetically controlled with an apparent activation energy of about 54.34 kJ/mol. A pseudo-homogeneous reaction model was developed for the acetalization reaction over the heterogeneous catalyst. The model could fit the experimental conversion–time data reasonably well. As a heterogeneous catalyst, the ion-exchange resin was recovered and then reused without reactivation six times. This is an eco-friendly process, and the catalyst can be recycled without regenerating.

Declarations

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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An overview on non-wood fiber characteristics for paper production: Sustainable management approach

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Abstract

The amount of paper and paperboard a country uses are a reliable barometer of its development. Having access to them is essential to our daily life. The Indian paper industry faces a number of challenges, one of which is a scarcity of high-quality raw materials. Agricultural waste products have become essential alternative sources of supply as a result of an increase in the need for fibrous raw materials, a global lack of trees, and a growing awareness of sustainability. When compared to the manufacturing of pulp and paper from wood sources, the use of non-wood sources (including bagasse, maize stalks, cotton stalks and rice straws) offers a number of advantages. These benefits include superior quality of the bleached pulp and excellent sources for specialty papers. Paper manufacture is more ecologically friendly and sustainable when non-wood fibers are processed since non-wood pulping technologies use less energy than wood-based pulping processes. Furthermore, the financial advantages include cost savings, market differentiation, enhanced sustainability, and access to government subsidies. By investing in non-wood fibers to satisfy rising customer demand for environmentally friendly goods, paper manufacturers may position themselves for long-term prosperity and

environmental responsibility. The non-wood fibers are cellular and have a complex cell wall structure. A thorough understanding of their properties is essential for effective use. Therefore, the objective of the present review is to explore the wide variation between critical characteristics (morphological, chemical, and mechanical) and the most appropriate pulping and bleaching processes for commonly used agricultural residues (Rice straw, Bagasse, Wheat straw and Bamboo) in the Indian pulp and paper industry for the production of paper, board, and packaging.

Introduction

Paper has revolutionized how we communicate, document history, and write literature. It is more portable, smaller and lighter than other materials. Even in this digital age, the role of paper remains essential, with this ubiquitous material still used daily for many purposes worldwide. It has prompted the development of new cleaning products, printers, and even food [1]. In 2020, the global paper and paperboard production volume was roughly 401 million tons. In India, around 759 pulp and paper mills are currently in operation, which is 4% of global paper production [2]. This industry is ranked as the world's 15th largest. The paper market is divided into four submarkets: board and packaging paper, writing and printing, newsprint and specialty papers [3]. Paper is an impermeable sheet that ranges in length from 0.25 to 4.5 mm and is made up of pulp fibers linked together as a three-dimensional network [4]. The lignocellulosic materials such as softwoods, bagasse, rice straw, bamboo and wheat straw are used to make pulp fibers [5]. These raw materials are chemically composed of cellulose (40–50%), hemicellulose (25–30%) and lignin (25–35%), with trace amounts of extractives, proteins, and inorganic compounds [6]. Cellulose is a highly organized linear polymer of D-glucopyranosyl-1,4-D-glucopyranose (cellobiose). Hemicellulose is a branching carbohydrate polymer comprising both pentoses and hexoses. Lignin, on the other hand, is a three-dimensional network comprising syringyl, S, guaiacyl, G and p-hydroxyphenyl, H phenylpropanoid units [7]. The primary application of lignocellulosic biomass is the production of cellulosic pulp, which may be used to make a variety of products, including paper.

In order to meet its need for fiber, the paper industry accounts wood for 30–35% agricultural wastes for 20–22%, and recycled fibers for 45–50%, respectively. The preparation of paper from non-wood fibers is shown in Fig. 1. Monoculture tree plantations are spreading across the tropical and subtropical regions, with the goal of producing controlled and homogeneous wood structures, resulting in easy availability of wood, a cost-effective process, and higher yields. To overcome raw material availability, the industry is also attempting to reduce plantation cycles from 54 to 42 months. High energy and electricity costs, environmental enterprises, specialized fustiness, and raw

material vacuity are just a few of the issues confronting the Indian paper industry. The most significant challenge is the failure of high-quality raw materials.

As the assiduity's wood force is insufficient due to a lack of government access-possessed forest areas, several opportunities exist to substitute woody fibers with non-woody or recycled fibers. Indian paper manufacturers have responded to the shortage of wood by launching efforts like agroforestry (farming method that involves combining agriculture with tree cultivation), which has spread rapidly across select regions of the country. Due to the flexible nature of cell walls, agricultural residue is more sustainable for paper production than wood fiber, according to assiduity specialists [8]. The agro residue requires less time to reuse than wood for the same cooking settings and pulp qualities, indicating that agro-biomass-derived paper consumes less water, fewer chemicals, and less energy [9]. Agro-based paper manufacturing is widely considered to be more sustainable and competitively priced than wood pulp production. A number of resources, such as agricultural waste, industrial crops, and naturally occurring plants, might be used to create substitutes for wood fibers [10]. Using pulp and paper made from non-wood materials as opposed to wood has a number of advantages, including the simplicity of pulping (process that turns raw materials like wood or recycled paper into pulp), the high quality of bleached pulp, and the availability of great sources for specialty papers [11].

The growth cycles of non-wood materials are faster than wood. For instance, bamboo, straw, hemp etc. has a short growing season and may be picked. As a result, paper mills may have a steady supply of fiber in less time, resolving the issue of a potential wood scarcity. Agro-based paper manufacture uses up to 90% less water and 60% less energy than traditional wood-based paper production. Also, Jiang et al. (2019) life cycle analysis revealed that employing bagasse, straw etc. for paper manufacture has a much lower environmental effect than using wood-based alternatives, including fewer greenhouse gas emissions and water use [12]. The most serious issue with using agricultural wastes is the presence of silica, which causes scale development in recovery boilers, evaporators, causticizing equipment and soda ovens [13]. The possible benefits as well as downsides related to the use of agro-based paper manufacture is shown in Table 1 to provide a balanced perspective [14], [15].

The 21st century has witnessed non-wood fibers emerge as a significant alternative source of fibrous material, driven by a confluence of factors such as increasing global demand for fibrous materials, tree scarcity in various regions, and growing environmental awareness. As a result, these alternative 'fiber sources' must be considered to address any potential shortage of wood for paper-making. Therefore, the current review concentrates on the wide variation between significant properties (morphological, chemical, and mechanical) and the appropriate pulping process of

commonly used agricultural residues (Bagasse, Wheat straw, Bamboo, and Rice straw) in the Indian pulp and paper industry for the production of paper, board, and packaging. The optimum sustainable management approach for non-wood fibers in papermaking is a synthesis of various crucial strategies that take economic, social, and environmental factors into account, such as [16], [17]:

- Reduce waste and optimize resource use across the supply chain.
- Encourage agroforestry and the use of crop wastes in papermaking to decrease environmental and agricultural waste.
- Promote the use of recycled fibers and emphasize paper recycling.
- Implement environmentally friendly production techniques in pulping and papermaking to decrease chemical usage and energy consumption.
- Invest in R & D to investigate sustainable fiber sources as well as improved pulping and papermaking processes.

Section snippets

Chemical composition of fiber species

Cellulose molecules fit snugly together over long segments, resulting in powerful associative forces and, eventually, great strength (Fig. 2). Paper derives its strength from cellulose, a polysaccharide, due to the narrower width (5–30nm) and fiber-aligned orientation of its microfibrils. A minor variation, measured as the microfibril angle (MFA), exists in this alignment [18]. Native cellulose in-situ has degree of polymerization values (weight average) as high as 3500 and can become …

Ultrastructure of cell wall

Understanding and controlling the ultrastructural changes that occur during pulp processing requires an understanding of the ultrastructural arrangement within fibers. Wood and non-wood are composed of cells, which are held together by lignin-rich

middle lamella. A cell wall and lumen make up each cell and is referred to as a fiber. As shown in Fig. 3, the lumen is considered to be void and exists as a central canal within the fiber. Lumen diameter is between 10 and 20μm, and cell wall …

Cell types

Non-woods are made up of several units called cells (Fig. 4).

- Short, compact, and stumpy best describes ***Parenchyma cells***. In comparison to fiber cells, water absorption is 15 times higher, so more liquid may be added during cooking. Parenchyma cells' efficient water absorption ensures improved fiber separation during pulping, increasing pulp production and aiding proper water distribution, affecting paper qualities like thickness, smoothness, and printability. The paper's strength and stability …

…

Pulping processes for non-wood raw materials

The binding substance lignin is eliminated from the middle lamella during the pulping process, and cells or fibers are separated. The cooking process for non-wood fibers now incorporates delignification technology, such as the (alkaline) kraft process, (acidic) sulphite process, soda process, organosolv pulping, chemi-mechanical pulping (CMP) and biological pulping, among others. Non-woods require less chemicals to remove the lignin from the fibers during cooking since they have a low lignin …

Bleaching of non-wood pulps

The inherent luminous reflectance factor at 475nm is what we refer to when we talk about brightness. By eliminating or altering the pulp's coloured components, the end goal of bleaching is to increase the pulp's brightness (Fig. 5). Lignin's chromophoric groups are mostly to blame for the pigmentation it displays. Some of the phenolic groups (in lignin) are oxidized to quinine-like compounds, which are known to absorb light. Before pulps are bleached, over 6% of the lignin remains. In general, …

Agricultural residues for pulp and paper making

The utilization of agricultural residues in the paper and pulp industry is widespread due to their abundance and availability. Because they include fibers with comparable and

average biometrical qualities to hardwood fibers, they are generally used in the paper industry. Furthermore, in addition to producing pulps and papers with denser and stiffer sheets, these agricultural wastes can also yield pulps that are simpler to drain for further processing [36]. Through the addition of chemicals and …

Morphological characteristics

The fiber morphology of a non-wood species is vital for determining its appropriateness for pulp and paper manufacture (Table 2). The longer the fibers, the greater the resistance of the paper to tearing [38]. Longer fibers, on the other hand, provide a more open and less uniform sheet structure. The average length and diameter of non-wood fibers are between 0.5 and 30mm and 8–30μm, respectively. Thin cell wall fibers collapse rapidly. Higher coarseness fibers are stiffer and more difficult …

Challenges and prospects

Due to rising paper demand and scarce wood supplies in emerging countries, non-wood pulp technology will advance rapidly. Wheat-Board, Prime Board, and Dura-Cane are examples of successful industrial applications of cellulosic agro-based waste. Yet, the depletion of pulping chemicals in black liquor and the unavailability of raw materials are the main downsides of using fiber sources other than wood in the pulp and paper business. Agro residue drains slower than softwoods due to shorter fibers. …

Conclusions

The existing wood supplies may not be sufficient to supply the rising demand for paper given the growth in paper consumption. Therefore, non-wood pulp must be taken into account to make up for any potential shortage of wood fiber needed for paper production. Because of this, there has been an increase in the development of alternative pulping technologies that are less harmful to the environment. Using non-wood fibers for papermaking offers financial benefits, including cost savings, market …

CRediT authorship contribution statement

Madhuri Pydimalla: Writing – original draft, Supervision, Conceptualization. **Hima Vamsi Chirravuri:** . **Appala Naidu Uttaravalli:** . …

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. …

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Experimental visualization of mass transfer from a slug bubble during co-current flow in a conventional channel

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High-speed imaging

ABSTRACT

Process intensification during gas–liquid flows is of paramount importance to optimize the size of the chemical reactors. This paper results from an investigation of the mass transfer visualization in a millimetric tube by using the colorimetric technique. A slug bubble train has been established in a 3.8 mm diameter tube for different gas superficial velocities and a constant liquid superficial velocity resulting in the low capillary number range between $0.0004 < Ca < 0.0006$. Color-inducing dye Resazurin solution interacts with the Oxygen bubble to induce the pink color in the solution which has been captured by a high-speed camera. The liquid slug entrapped between the bubbles has three distinct regions namely, the central stem which has a stagnation point ahead of the bubble, the wall lubrication layer, and an entrapped Taylor vortex between the central stem and wall lubrication layer. Flow visualization results have been correlated with the penetration theory-based mass transfer models.

1. Introduction

Gas-liquid mass transfer and hydrodynamics find applications in various fields ranging from blood flow in the pulmonary capillaries (Prothero and Burton, 1961), water filtration by using gas sparging in ultrafiltration hollow fibers (Laborie et al., 1999), monolith slurry reactor (Boger et al., 2003), monolith mass transfer reactors (Kreutzer et al., 2005; Haase et al., 2020; Rollbusch et al., 2015; Kastens et al., 2015), Carbon dioxide absorbers (Madhavi et al., 2007; Hosoda et al., 2014; Sa'adiyah et al., 2021; Hayashi and Tomiyama, 2018), microbubbles dynamics (Tanaka et al., 2020) and the reduction of syngas to the hydrocarbons by using Fischer-Tropsch process (Maretto and Krishna, 1999).

The mass transfer from the bubble is closely coupled with its hydrodynamics. Higbie penetration theory (Van Elk et al., 2007; Samanta and Bandyopadhyay, 2007) simply presented the liquid film replenishment model in which each fluid element is exposed to the gas interface before being replaced by the other (Kreutzer et al., 2005). The liquid side mass transfer coefficient, $k_l = 2\sqrt{D_{gas}/\pi\tau}$, where D_{gas} (m^2/s) is the diffusivity of the gas in the surrounding fluid and τ (s) is the contact time of the fluid element with the gas. Therefore, the flow pattern and the liquid hold-up in the closed conduits are of paramount importance in the quantification of the mass transfer performance. In industries, monolith reactors are preferred for performing mass transfer operations due to their regular honeycomb structure, controlled phase distribution, relatively less pressure drop, low energy consumption, and absence of moving parts (Kreutzer et al., 2005; Sobieszuk et al., 2012; Haase et al., 2016; Butler et al., 2018; Abiev et al., 2019; Bauer et al., 2006).

A subset of the problem in designing the mass flow reactors is to identify the flow pattern and contact time between the two phases. Taylor/slug flow pattern is a very common flow feature in monolith reactors. The flow channel in the monolith reactor could be of either millimetric size or micro-metric size based on the required specifications of the output liquid composition. A simplified criterion to decide the capillary behavior of the conduit is the Bond number, $Bo = \Delta\rho g d^2/\sigma$ which is nothing but the balance between the buoyancy forces and the capillary forces. For the current investigation, the length scale for $Bo \sim 1$ is $l_c = \sqrt{\sigma/\Delta\rho g}$ $1.89mm$, which indicated that our mass transfer absorber is working in the millimetric regime. Taylor (1961) described the presence of the recirculation and bypass regime during the co-current flow in a capillary based on the parameter, m. Taylor's work advocated that there is only one stagnation point present at the nose of the slug bubble for $m > 0.5$ and two stagnation points are present when $m < 0.5$. The two stagnation points result in the recirculation inside the liquid slug which is entrapped between the two consecutive bubbles.

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Nomenclature

$(k_{gl}a_{gl})_{overall}$	Overall gas–liquid mass transfer coefficient (s^{-1})
$\forall_g$	Volume of gas (m^3)
$\forall_l$	Volume of unit cell (m^3)
A_b	Cross section area of the bubble (m^2)
C^*	Saturated concentration of the Oxygen in the water (g/l)
Ca_{U_b}	Capillary number base upon in-situ gas velocity (dimensionless),$\mu_l U_b/\sigma$
Ca_{tp}	Capillary number based upon two phase flow velocity (dimensionless),$\mu V_{tp}/\sigma$
D_{O_2}	Diffusivity of Oxygen in water,(m/s)
D_3	Diameter of the central stem (m)
D_{gas}	Diffusivity of gas in liquid (m^2/s)
L_{UC}	Length of the unit cell (m)
L_b	Length of the bubble (m)
L_b	Length of the gas bubble (m)
L_l	Length of the liquid slug (m)
N_{O_2}	Mass flux of the Oxygen normal to the interface $(kg.m^{-2}s^{-1})$
Q_b	Gas flow rate,(m^3/s)
R_1	Radial distance from the axis of the tube to the wall lubrication layer (m)
Re_b	Bubble Reynolds number (dimensionless),$(\rho_l-\rho_g)DU_b/\mu_l$
Re_b	In-situ bubble velocity-based Reynolds number (dimensionless),$(\rho_l-\rho_g)DU_b/\mu_l$
Re_{film}	Film Reynolds number (dimensionless),$(U_{film}\delta_{film}\rho_l)/\mu_l$
Re_s	Slug Reynolds number (dimensionless),$(\rho_l-\rho_g)DU_s/\mu_l$
R_o	Radial distance from the axis of the tube to the centre of the Taylor vortex (m)
U_b	In-situ gas velocity (m/s)
U_{film}	Annular film velocity (m/s)
U_m	Velocity of the liquid slug ahead of the slug bubble (m/s)
U_s	In-situ liquid slug velocity (m/s)
V_g	Gas superficial velocity (m/s)
V_l	Superficial velocity of the liquid (m/s)
V_{tp}	Two phase superficial velocity (m/s)
a_{cap}	Area of hemispherical bubble cap (m^2)
a_{film}	Surface area of the annular film (m^2)
a_{gl}	Gas liquid interfacial area per unit volume (m^2/m^3)
$c_{O_{2,b}}$	Concentration of the Oxygen in the liquid away from interface
$c_{O_{2,i}}$	Concentration of the Oxygen at the gas–liquid interface
d_{eq}	Volume equivalent bubble diameter (m)
k_l	Liquid side mass transfer coefficient (m/s)
l_c	Capillary length scale (m),$\sqrt{\sigma/\Delta\rho g}$
q_2	Discharge through the central stem (m^3/s)
t_{film}	Film contact time scale (s)
w_2	Velocity of the fluid in the central stem (m/s)
w_z	Axial circulation relative velocity (m/s)
δ_{film}	Annular film thickness of the bubble (m)
ε_o	Initial void fraction of the bubble (dimensionless)
μ_l	Dynamic viscosity of the liquid $(Pa.s)$
ρ_g	Density of gas (kg/m^3)
ρ_l	Density of liquid (kg/m^3)
ΔGV	Grey value difference (dimensionless)
Bo	Bond number (dimensionless),$\Delta\rho g d^2/\sigma$
C	Dissolved Oxygen concentration (g/l)
C^*	Saturated Oxygen concentration (g/l)
$C(z)$	Concentration profile in the liquid slug (g/l)
D	Tube diameter (m)
Fo	Fourier number (dimensionless),$D_{O_2}t_{film}/{\delta_{film}}^2$
J	Modified parameter for deciding circulation or bypass regime (dimensionless)
R	Capillary tube radius (m)
We	Weber number (dimensionless),$\rho_l {U_b}^2 D/\sigma$
c	Concentration of Oxygen (g/l)
f	Liquid recirculation frequency (Hz)
g	Acceleration due to gravity (m^2/s)
m	Parameter for circulation or bypass regime (dimensionless)
n	Number of moles $(mole)$
$u(x)$	Relative velocity of the liquid slug with respect to the bubble (m/s)
x	Radial location in the tube (m)
z	Axial distance normal to the gas–liquid interface (m)
α	In-situ void fraction of the gas (dimensionless)
β	Superficial void fraction (dimensionless)
θ	Interfacial angle of rotation $(radians)$
λ	Ratio of the equivalent bubble diameter to the tube diameter (dimensionless)
σ	Interfacial tension between gas and liquid (m)
τ	Contact time of the fluid element with the gas (s)

Subscripts

b	Bubble
cap	Cap of the bubble
eq	Equivalent
$film$	Film
g	Gas
l	Liquid
s	Slug
tp	Two-phase

Therefore, the establishment of the flow pattern in the Taylor flow regime could vary based on the relative value of m which could have repercussions on the mass transfer performance. The pioneering work by Goldsmith and Mason (1963) included the measurement of the film thickness around the bubble inside a capillary and reported the recirculation criterion proposed by Taylor (1961). Cox (1964) provided concrete proof of the hypothesis made by Taylor (1961) regarding the recirculation regime and bypass regime. The experiments by Cox (1964) very well established the presence of the dividing streamlines in the entrapped liquid slug. Repercussions of the presence of the recirculation regime could be more profound in the presence of the Marangoni stresses. Kreutzer et al. (2005) reported the presence of the surfactant concentration around the slug nose along with the change in the direction of the tangential stresses. The concentration of the surfactant makes the slug cap immobile and changes the effective boundary condition at the gas–liquid interface, which eventually affects the shape of the gas bubble cap.

A similar flow structure (recirculation or bypass) in the liquid slug has also been observed at a millimetric scale during the PLIF-I-based laser investigations (Butler et al., 2016; Abiev et al., 2019) and colorimetric investigation (Krieger et al., 2020). Abiev et al. (2019) employed a three-layer model to distinguish the flow distribution in the entrapped liquid slug of a circular tube. Earlier, Abiev (2009) slightly modified the criterion provided by Taylor (1961) for the transition between the bypass and recirculation regime by noticing the presence of the Poiseuille flow in the liquid slug. The parameter, $J = \{2-(U_b/V_l)\}$ is the

new criterion for which there is the presence of the recirculation regime in the capillary at $J > 0$ and the streamlines simply bypass the gas slug for $J < 0$ (Abiev and Lavretsov, 2012). The parameter, J characterizes the relative slip between the gas and the liquid slug (Abiev and Lavretsov, 2011). Abiev et al. (2019) demonstrated the presence of the three layers in the liquid slug namely, the wall lubrication layer along the channel wall (layer 3), the central stem which has either one or two stagnation points (layer 1), and finally, the bulk Taylor flow entrapped between the wall layer and the central stem (layer 2). Recently, Abiev (2020) detailed the three layers in a liquid slug for a millimetric channel along with the analytical models for the prediction of the overall mass transfer coefficient.

In this paper, we have extended the colorimetric technique proposed by Dietrich et al. (2013) and Kherbeche et al. (2012) for studying the mass transfer mechanism in the co-current slug flows. The colorimetric technique provides the advantage of quick bubble film and liquid slug scale analysis inside the circular tube. In industries, it is generally not possible to deploy sophisticated PLIF-I technology which involves precision lasers. The colorimetric technique provides an online analysis of the mass transfer process quantification contrary to the delay incurred during the offline quantification technique like spectroscopy. Furthermore, colorimetric techniques are employed in the gas–liquid stirrer reactors for direct visualization and scale-up (Piccione et al., 2017). The objective of the paper is to observe the characteristic three-layer structure during the co-current flow which is generally observed during the numerical simulations or resource intensive laser-based techniques (PLIF or μ-PIV). The three-layer structure has been validated with the analytical expressions deduced by Abiev et al (2019). Moreover, the bubble bypass regime and recirculation regime proposed by the classical works of Cox (1964) and Taylor (1961) have been observed experimentally by keeping the low capillary numbers.

The rest of the paper is organized as follows, section 2 consists of the details about the experimental apparatus, thermophysical properties of the fluid, image analysis, and principle of colorimetric technique. Section 3 consists of the results and discussion on co-current flow hydrodynamics, comparison with the three-layer model, visualization of the slug bubble train, and modelling of liquid side mass transfer coefficient by penetration theory. Finally, section 4 consists of the conclusion and summary of the results from the proposed study.

2. Experimental methods and thermophysical properties of the fluids

2.1. Co-current flow visualization apparatus

The experimental apparatus consists of a vertical glass tube with a 3.8 mm internal diameter. Referring to Fig. 1, the glass tube has been treated with the piranha solution to make it hydrophilic. The glass tube has been fixed in the robust frame with the phase distributor (Fig. 1, inset). Co-current flow has been established in the tube by pumping an Oxygen sensitive dye Resazurin (Brand: HiMedia, 7-Hydroxy-3H-phenoxazin-3-one-10oxide sodium salt, $C_{12}H_6NNaO_4$, molecular weight = 251.17 gm/mole, purity 80%, CAS 62758–13-8) based solution along with pure medical grade Oxygen (gas density, $\rho_g = 1.4 kg/m^3$; gas viscosity, $\mu_l = 2.04 \times 10^{-5} Pa.s$ at NTP, 99.5 % v/v). The apparatus has been kept in the open inside the lab with appropriate ventilation eliminating the fire hazard due to the pure Oxygen. The bubble train achieves steady state earlier at the low capillary numbers and Weber number as compared to the higher Weber number and capillary number cases in which liquid inertial effects could be dominant. The camera and the view box have been kept at the 230 mm mark in the tube which is sufficient distance for the annular film to develop and achieve the steady state (46 % of the tube length). Moreover, the experiments have been conducted in the laminar regime with Reynolds number, $Re_b = (\rho_l - \rho_g)DU_b/\mu_l =$ 101.5 – 150.0, therefore, the possibility of the coalescence between the bubbles of the slug train is very low. The periodicity of the gas–liquid slug train also depends upon the phase distributor

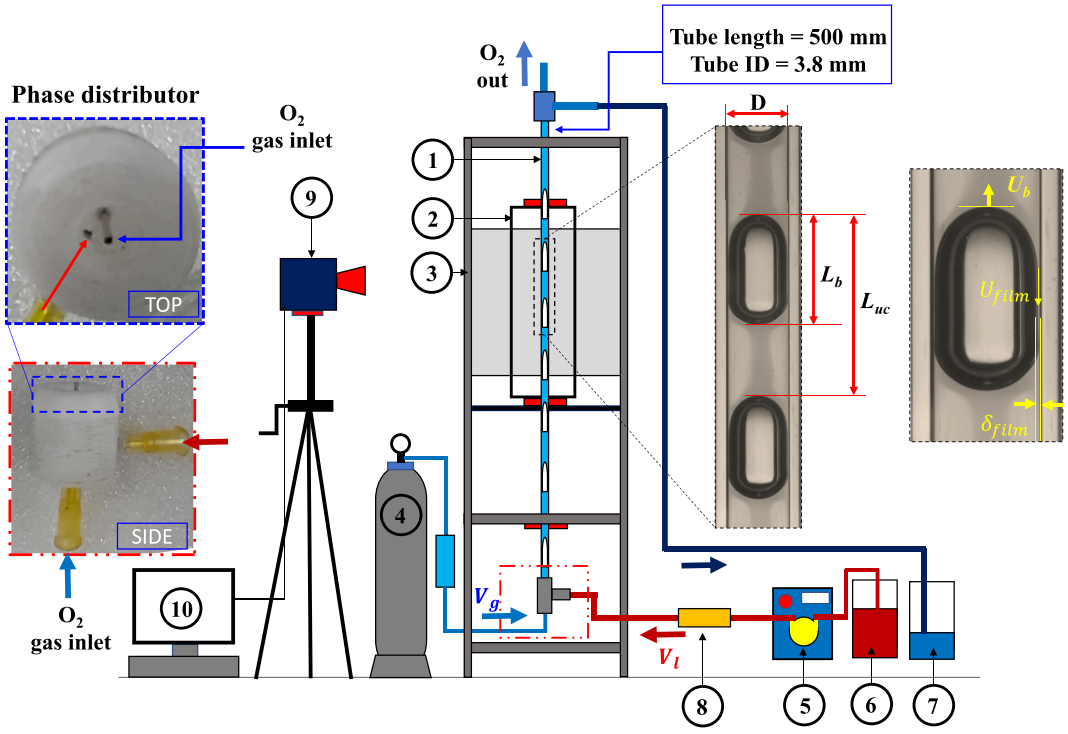

Fig. 1. Schematic diagram of the co-current experimental apparatus for mass transfer visualization, (1) reactor tube, ID = 3.8 mm, (2) view box, (3) holding stand, (4) Oxygen cylinder, (5) peristaltic pump, (6) resazurin dye solution, (7) Oxygenated solution, (8) mass flow meter, (9) high-speed camera, (10) computer. The inset figure shows the slug bubble train along with the phase distributor and anatomy of the slug bubble (note: image not to scale). L_b represents the gas slug length and L_{uc} represents unit cell length.

utilized to introduce the liquid and the gas into the millimetric channel. We had designed a special phase distributor which has been shown in the new inset of Fig. 1, which allowed us to remove the inlet effects caused due to maldistribution of the phases in the channel. The coalescence between the slug bubbles has not been observed during the laminar regime with the in-house designed phase distributor. The experimental cases and their hydrodynamic parameters have been summarized in Table 2. Table 2 shows the in-situ void fraction, α, superficial void fraction, β, gas superficial velocity, V_g, two phase superficial velocity, V_{tp}, length of liquid slug, L_l, bubble length, L_b, in-situ gas velocity, U_b, liquid superficial velocity, U_s.

All the experiments have been performed at a constant liquid superficial velocity, $V_l = 0.016m/s$. The main aim of the investigation is to test the presence of the three-layer structure by using the Resazurin dye method. Therefore, the superficial velocity of the liquid has been kept constant and only the superficial velocity of the gas has been varied to get different slug length and Taylor Vortex structure in the intermittent liquid slug.

The slug bubble is devoid of any inertial effect at low capillary numbers, Bond number and Weber number due to which its annular film remains symmetric. The interfacial reconstruction step in our investigation required the presence of the axisymmetric nature of the bubble. Therefore, we have conducted our investigation with only a single liquid superficial velocity.

The dye solution passes through a filter before entering the circular tube. The pressure of the oxygen gas at the inlet of the tube has been adjusted to achieve different gas superficial velocities. The residual solution is collected in a separate beaker after the separation of the Oxygen gas. A view box filled with glycerol solution has been constructed around the tube to avoid optical distortion issues. The Oxygen sensitive dye reacts with the Oxygen gas present in the injected bubble. The dissolved oxygen in the dye solution is highlighted with the shedding of pink color from the bubble. To prepare the solution, Sodium hydroxide (Brand: HiMedia, CAS 1310–73-2) and pure Glucose (Brand: HiMedia, CAS 50–99-7) have been diluted with deionized water to achieve a concentration of 20 gL^{-1} each. A fixed concentration of the resazurin dye (0.1 gL^{-1}) has been added to the mixed solution of pure glucose and sodium hydroxide resulting in the liquid dye solution for the experiments. Similar concentration and proportion of solute concentration has been used by Kherbeche et al. (2013) and Dietrich et al. (2013), therefore, we have used same diffusivity of Oxygen as their study. The other thermophysical properties of the resazurin dye solution are shown in Table 1. The surface tension of the fluid has been measured Kruss type Goniometer by pendent drop method and the viscosity has been measured by plate-cone type rheometer. The colorimetric technique is used in this study to identify the dissolution of the Oxygen from the slug into the surrounding liquid. The brief overview of the principle of the colorimetric technique has been described in the Appendix 1.

2.2. Image processing, interface extraction, and concentration contours

High-speed photography (Model: CHRONOS 2.1, make: Canada) is utilized to capture the flow field around the slug bubble train (Fig. 2(a)) at 1000 frames per second. The image analysis has been done with in-house written image analysis codes in MATLAB (Rohilla and Das, 2019; Rohilla and Das, 2020). The slug bubble train image is subtracted from the background image (Refer to Fig. 2(a) and (b)). The greyscale image is necessary for mask reconstruction in the concentration detection step.

The grey scale image is converted to the black and white image with a threshold. Thresholding is selected to detect the interface of the bubble only. The holes in the image have been removed by processing (Fig. 2 (d)). Thresholding partitions the image into the background with black color and bubble with white color (Fig. 2(e)). The detected interface in the slug bubble train is shown in Fig. 2(f).

The background is subtracted from the image leaving only the color emanating from the bubble with all surrounding grey values to zero (black color). The detected interface is utilized to reconstruct the white mask and camouflage the bubble from the calibration calculations (Fig. 2(g)). The extracted interface coordinates from the image analysis have been further utilized to generate a three-dimensional reconstruction of the bubble (Fig. 3). A simplified coordinate transformation has been implemented to reconstruct the interface from the experimental analysis (Fig. 3(a-c)). Initially, the coordinates of the bubble interface are extracted. Since the bubble remains axisymmetric in the current investigation. The half section of the coordinates is considered for the axisymmetric rotational transformation. The next coordinates are predicted with $\Delta\theta = 0.02radians$, implemented with the transformation matrix show in Fig. 3. The whole $\theta = 2\pi$ is covered with the steps of $\Delta\theta = 0.02radians$. The inhouse MATLAB code performs this process of axisymmetric rotation and the resulting interface is deduced in the form of an STL format file. The volume inside the bubble has been computed by first making the mesh in the STL format file and computing the volume of each mesh element. Furthermore, the interfacial area of the bubble has been computed by importing the STL file in the paraview software. Fig. 4(a) shows the mapping between the grey scale value difference, ΔGV and equivalent Oxygen concentration. The difference in the grey scale intensity, ΔGV is the absolute difference between the grey value of the deionized water sample and the resazurin dye dissolved sample. A linear relation has been observed between the dissolved Oxygen concertation, C and the grey value difference, ΔGV. Similar linear relation has been observed during the earlier studies by Kherbeche et al. (2013) and Dietrich et al. (2013) during gas–liquid interactions. Refer to Fig. 4(a) inset, the tube section is divided into four different sections (shown as sections A to D) which results in the different calibration curves mapping the grey scale value difference and equivalent Oxygen concentration. Section A consists of a slice of length $0.25D$ from the tube central axis, section B consists of a slice of length $0.12D$ after section A, section C is of length $0.06D$ after section B and finally, the remaining tube section has been calibrated as section D (Fig. 4(a), inset). Mei et al. (2020) have proposed pixel-by-pixel calibration technique which would provide better radial concentration plots. The current 4-section calibration assumption does introduce a major approximation, however, as a preliminary attempt we have implemented the same to derive the radial concentration plot which assumes the same calibration curve for a certain section of the tube.

Fig. 4(b) shows the implementation of the calibration curve to the greyscale images. The grey scale value for the image ranges from 0 to 255. The grey scale bubble has been masked with white color to remove it from the calculations by thresholding. The measurement of the dissolved concentration around the bubble requires a priori knowledge of the grey scale value at different resazurin concentrations. Different resazurin concentration results in different sample color due to the differential dissolution of the oxygen. The samples ranging from 0 to 0.025 g/litre of resazurin have been prepared under the standard lab conditions with deionized water and were allowed to uptake oxygen from the ambient for 48 h (Fig. 4(a) inset). These samples were filled in the experimental apparatus and the grey scale value of the glass tube region has been taken. It must be noted that the calibration thus performed is only valid for the specific geometry, light intensity, and camera settings. A new calibration curve may be deduced with the change in any of the above-mentioned parameters.

Table 1
Thermo-physical properties of the test fluids at $25 \pm 0.1°C$.

Thermo-physical properties	Value
Density, ρ_l ($kg.m^{-3}$)	1004.5
Surface tension, σ ($N.m^{-1}$)	0.075
Viscosity, μ_l(mPa.s)	1.118
Diffusivity of Oxygen, D_L (m^2/s)	2.1×10^{-9}

Table 2
Co-current flow parameters for the experiment.

S.no	α	β	V_g(m/s)	V_{tp}(m/s)	L_l(mm)	L_b(mm)	U_b(mm)	U_s(mm)
1	0.315	0.352	0.0092	0.0253	9.9	6.2	0.0283	0.0235
2	0.337	0.374	0.0101	0.0262	8.7	6.1	0.0284	0.0242
3	0.368	0.391	0.0108	0.0269	9.6	7.4	0.0279	0.0254
4	0.371	0.434	0.0129	0.0290	9.6	7.4	0.0330	0.0256
5	0.386	0.441	0.0133	0.0293	8.4	7.1	0.0325	0.0261
6	0.414	0.465	0.0147	0.0307	6.8	6.7	0.0338	0.0273
7	0.442	0.488	0.0161	0.0320	6.0	6.8	0.0348	0.0286
8	0.443	0.497	0.0167	0.0326	6.2	6.9	0.0359	0.0287
9	0.446	0.488	0.0161	0.0320	6.4	7.2	0.0342	0.0288
10	0.485	0.501	0.0169	0.0328	5.5	7.4	0.0333	0.0309
11	0.447	0.506	0.0173	0.0332	5.9	6.8	0.0372	0.0288
12	0.466	0.518	0.0182	0.0340	5.6	7.0	0.0376	0.0298
13	0.473	0.507	0.0173	0.0332	5.4	7.0	0.0346	0.0302
14	0.501	0.534	0.0193	0.0352	4.7	7.0	0.0369	0.0318
15	0.504	0.540	0.0198	0.0357	5.5	7.9	0.0372	0.0321
16	0.488	0.554	0.0209	0.0367	6.1	8.0	0.0403	0.0311
17	0.527	0.576	0.0228	0.0386	5.4	8.4	0.0413	0.0336
18	0.547	0.576	0.0229	0.0387	4.5	7.9	0.0397	0.0350
19	0.512	0.574	0.0226	0.0385	5.5	8.1	0.0418	0.0326

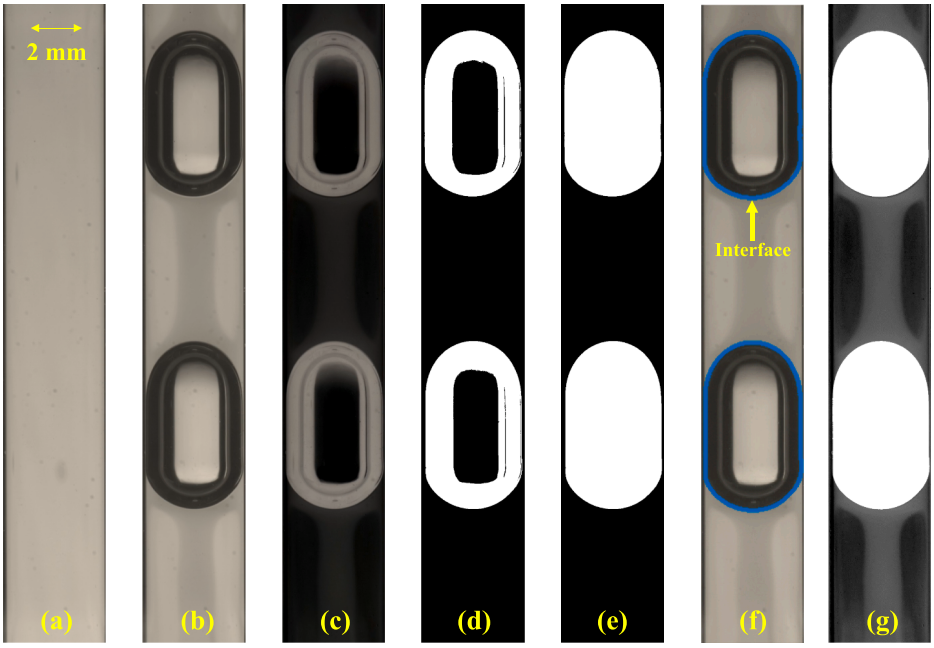

Fig. 2. Interface detection and masking technique for bubbles, (a) Image background, (b) slug bubble train, (c) greyscale image, (d) background subtracted greyscale image and converted to binary, (e) holes removed image, (f) detected image interface superimposed over the monochromatic image, (g) Subtracted greyscale image with bubble masking.

3. Results and discussions

The hydrodynamics of the slug train require quantification before analyzing the mass transfer performance of the channel. Taylor bubble is a simplified interface that could be captured by a high-speed camera and the flow regime could be quantified by the separated flow models.

The next sections discuss the slug bubble train hydrodynamics, validation of the three-layer model, and modelling of the overall mass transfer coefficient and radial concentration contours in the liquid slug.

3.1. Hydrodynamics of slug bubble during co-current flow

Bretherton (1961) studied the dynamics meniscus in the capillaries and provided the correlation for the annular film thickness around the gas-slug. In the current investigation, we have kept the parameter like the Bretherton's experiment ($Ca_{U_b} < 1$, $We < 1$ and $Bo < 1$) with in-situ bubble velocity based capillary number, $Ca_{U_b} = \mu_l U_b/\sigma = 0.00042 - 0.00062$, Weber number, $We = \rho_l {U_b}^2 D/\sigma = 0.0407 - 0.0890$ and Bond number as, $Bo = (D/2)^2/\left(\sqrt{\sigma/\rho g}\right)^2 = 0.474$.

All the experiments have been conducted in these parametric range. These conditions allow the implementation of the correlation for the annular film thickness, $\delta_{film}/R = 1.34(Ca)^{2/3}/1 + (2.5 \times 1.34(Ca)^{2/3})$ by Bretherton (1961) and Aussillous and Quere (2000).

The length of the gas bubble, L_b and the length of the liquid slug is the parameter of paramount importance which governs the mass transfer dynamics in a channel. The void fraction, β based upon the superficial velocities could be easily measured during the experiments. The relation between the in-situ void fraction, α and the superficial velocity based void fraction, β dictates the distribution of the phases in the channel. Generally, $\alpha < \beta$ due to which we have slip between the phases. The gas bubble in-situ velocity is slightly higher than the in-situ liquid slug ve-

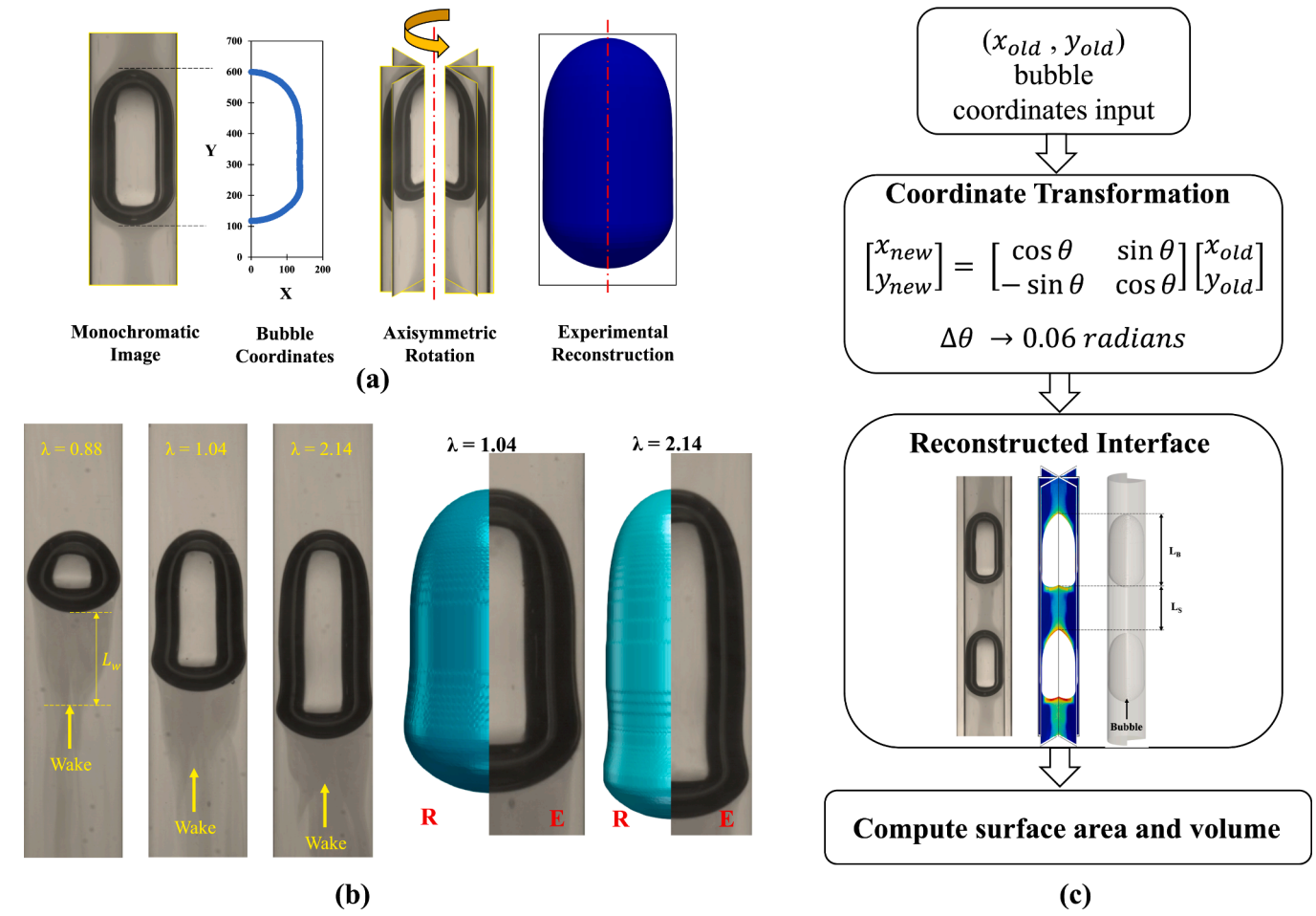

Fig. 3. Experimental interfacial reconstruction process of the slug bubble, (a) Interfacial coordinate extraction from the image analysis, (b) Comparison of the experimental reconstruction and the experiment slug bubble at different $\lambda = d_{eq}/D$ where d_{eq} is the volume equivalent diameter of the bubble and (c) Axisymmetric rotation algorithm for the extraction of bubble surface area and volume.

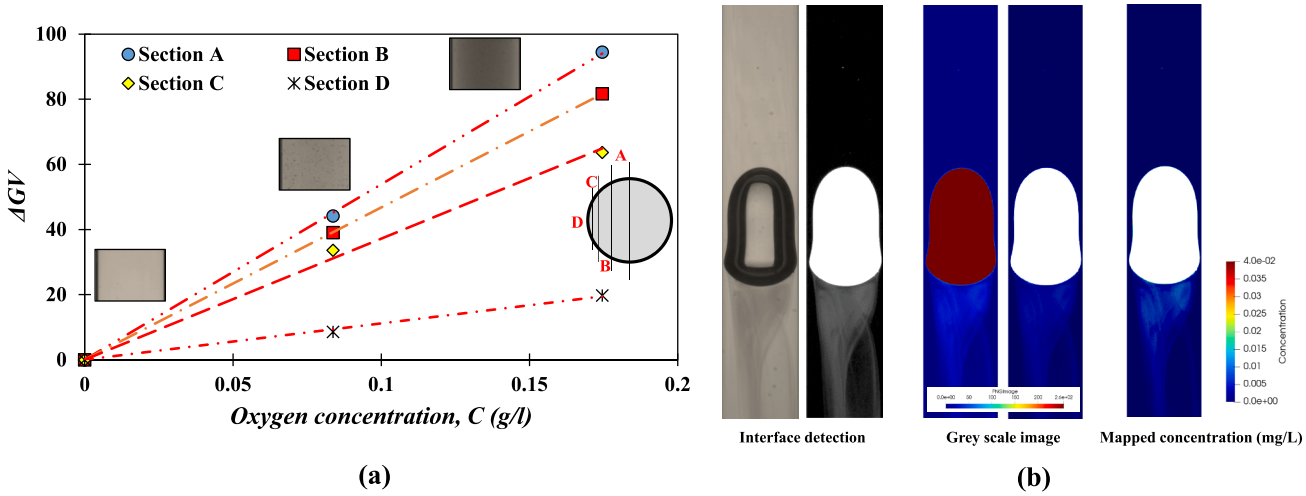

Fig. 4. (a) Calibration curve for different resazurin concentrations for mapping grey scale value difference, ΔGV and Oxygen concentration, C (g/l) at different tube sections and (b) Mapped concentration plot after the implementation of the calibration curve.

locity. The in-situ bubble velocity, U_b based on Reynolds number, $Re_b = (\rho_l - \rho_g)DU_b/\mu_l$ and in situ liquid slug velocity, U_s based on Reynolds number, $Re_s = (\rho_l - \rho_g)DU_s/\mu_l$ along with void fraction, β would be utilized to model the length of the unit cell, L_{uc}. The ratio of bubble length and liquid slug length, L_b/L_l could be modelled by a simple expression (Fig. 5(a), Eq. (6)).

$$L_b/L_l = 0.000208\beta^{1.026}Re_b^{-0.553}Re_l^{2.751} \quad (6)$$

Furthermore, a simplified log–log relationship exists between the

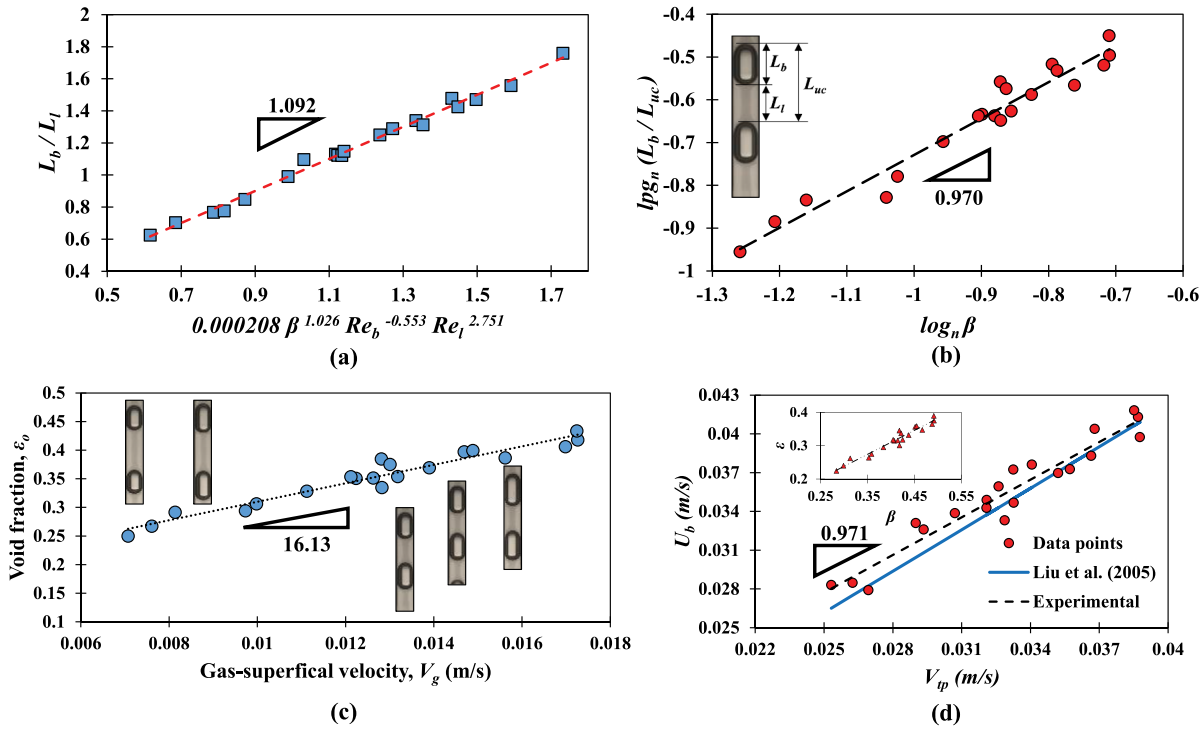

Fig. 5. (a) Empirical model for the ratio of bubble length to the liquid slug length, (b) Natural log–log plot for the variation of the ratio of L_b/L_{UC} with void fraction, β, (c) Variation of the in-situ void fraction, ε with the gas superficial velocity, and (d) Linear variation of the in-situ gas slug velocity with the in-situ two-phase velocity, V_{tp} (inset figure shows the variation of in-situ void fraction, α with superficial velocity-based void fraction, β).

ratio of bubble length and unit cell length, L_b/L_{UC} (Fig. 5(b); Eq. (7)).

$$\ln(L_b/L_{UC}) = 0.850\ln\beta + 0.1215 \tag{7}$$

Eq. (6) and (7) could be utilized to deduce the gas bubble length, L_b, unit cell length, L_{uc} and liquid slug length in terms of superficial velocity-based void fraction, $\beta = V_g/(V_g+V_l)$, and in-situ velocity-based Reynolds number. A linear relation has been found between the gas superficial velocity, V_g and in-situ void faction (Fig. 5(c)), $\alpha = \forall_g/(\forall_g+\forall_l)$, where, $\forall_g$ is the volume of gas and $\forall_l$ is the volume of the unit cell with length, L_{uc} (Fig. 5(b), inset). Similarly, the in-situ bubble terminal velocity, U_b varies linearly with the two-phase superfical velocity, V_{tp} (Eq. (8)). The inset in Fig. 5(d) shows the variation of the in-situ void fraction, α with the superficial velocity-based void fraction, β.

$$U_b = 0.971V_{tp} + 0.0034 \tag{8}$$

The in-situ velocity of the bubble, U_b varies linearly within the investigated range of the capillary number, $Ca_{tp} = \mu V_{tp}/\sigma = 0.00037 - 0.00057$. Liu et al. (2005) provided the correlation between the ratio of in-situ velocity and two-phase superficial velocity with the characteristic capillary number as $U_b/V_{tp} = 1/\{1-0.61Ca_{tp}^{0.33}\}$. Fig. 5 (d) shows the comparison between the Liu et al. (2005) model and the current experimental results. The additional buoyancy forces on the bubble causes them to move faster as compared to the liquid slug, therefore there is a difference between, U_b and V_{tp}.

3.2. Three-layer model for liquid slug hydrodynamics

Abiev et al. (2019) proposed the three-layer model for analysing the hydrodynamics of the co-current slug flows in the millimeter channel of 3 mm diameter in the laminar flow regime. Poiseuille parabolic velocity profile has been assumed in the liquid slug entrapped between the gas slug bubble train. The relative velocity in the liquid slug with respect to the rising bubble is given by, $u(x) = 2V_{tp}\left[1-4(x/D)^2\right] - U_b$. The velocity of the fluid in the central stem, $w_2 = q_2/A_2$, where $q_2 = 2\pi\int_0^{D_3/2} u(x)rdr$ is the discharge in the central stem and $A_2 = \pi(D_3/2)^2$ is the cross-section area of the central stem (Fig. 7(a)).

Similarly, the velocity in the other layers, w_1 and w_3 could be deduced in a similar (Abiev, 2013). Abiev (2013) proposed that the axial circulation velocity, w_z in the liquid slug about the radius, R_o is equal to the velocity of the fluid element between the radiuses, R_1 and R_o (Fig. 6 (a)). The axial circulation relative velocity is defined as, $w_z = -w_1 = w_2 = V_{tp} - (U_b/2)$ (Fig. 8(b)). The whole liquid slug can be divided into three regions, namely, the central stem layer, the Taylor vortex layer, and the lubrication wall film layer. The radius, R_1 is the radial distance from the axis of the tube to the wall lubrication layer and radius, R_o is the radial distance from the axis of the tube to the center of the Taylor vortex. Butler et al. (2018) reported the finding of Thulasidas et al. (1997) for the wall film radius, $R_1 = (d/2)\sqrt{\{2-(U_b/V_{tp})\}}$ and Taylor vortex radius, $R_o = (R_1/\sqrt{2})$. There is a similarity between the flow structure in the capillary and the millimeter tube during the co-current flow. The wall lubrication layer and the radius of the Taylor vortex could be measured from the pink color in the liquid slug. Fig. 6(b) shows the normalized central stem thickness, $D_3/D = 0.324$ and normalized wall film thickness, $\delta_{wall}/D = 0.0579$ with the two-phase superficial velocity, $0.025 < V_{tp}(m/s) < 0.038$. The deduced values for radius, R_1 and R_o from the image, analysis has been compared with the mathematical model described above and has provided satisfactory results (Fig. 6(c)). The error in the measurement of the layers thickness is of the order of one-pixel equivalent physical length scale i.e., $12.54\mu m$. Therefore, the uncertainty in the measurement of the layer's radii is $\pm 12.54\mu m$. Fig. 6(a) shows the schematic of the tube during co-current flow in circulation and bypass regime. The circular regime and bypass regime were initially proposed by Taylor (1961) and were experimentally observed by the seminal work of Cox (1964). They proposed a parameter, $m = (U-U_m)/U$, where U is the in-situ bubble velocity and U_m is the velocity of the liquid slug ahead of the slug bubble under

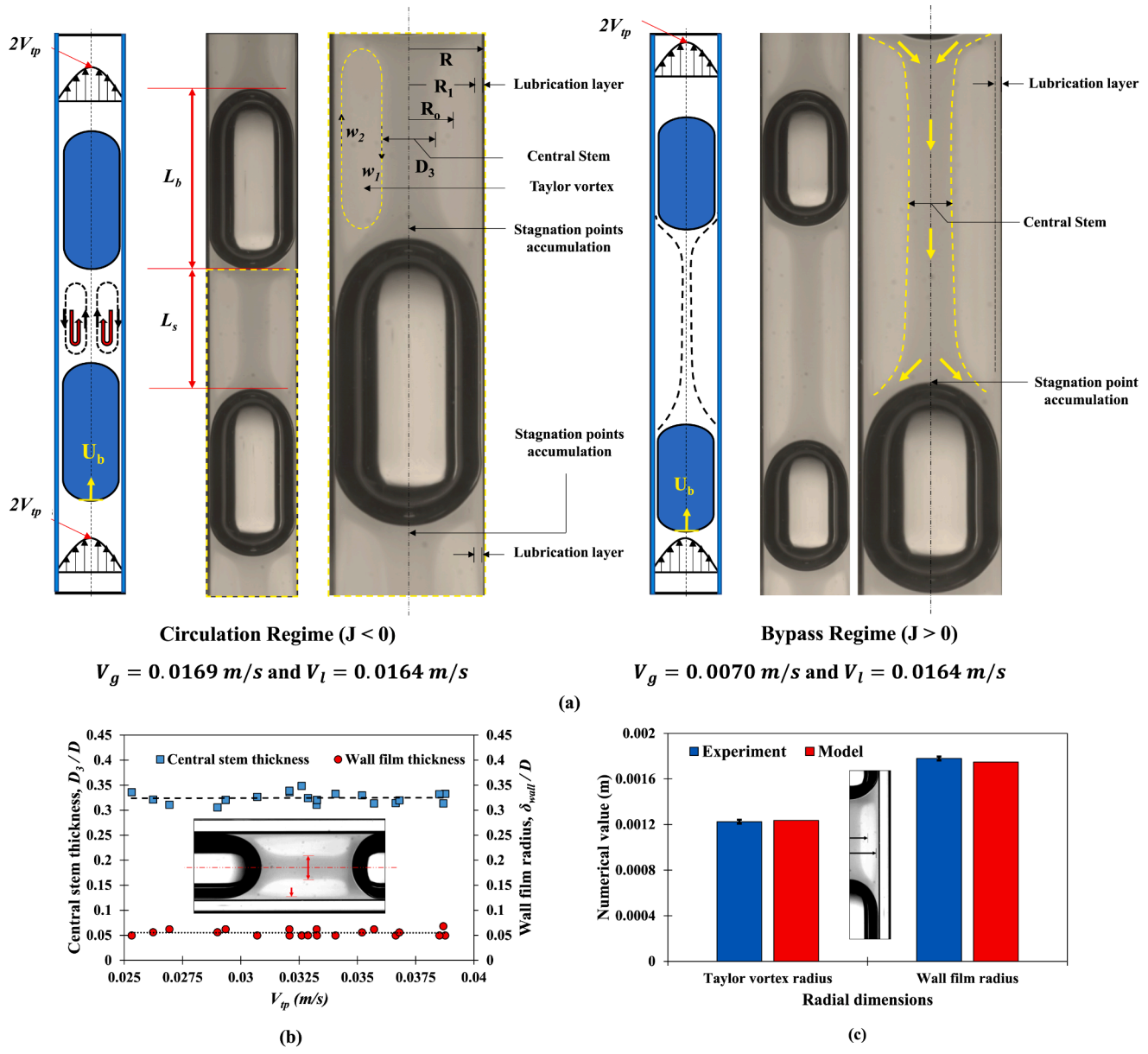

Fig. 6. (a) Schematic and physical description of the circulation ($J < 0$) and bypass regimes ($J > 0$), (b) Normalized central stem thickness and wall film thickness variation with the two-phase superficial velocity, and (c) Comparison of the three-layer model with the experimentally deduced Taylor vortex radius and wall film radius, inset figure shows the Taylor vortex radius and wall film radius during the co-current flow.

consideration. Taylor (1961) originally proposed the parameter, $m = 1.0(\mu U/\sigma)^{1/2}$ for the transition between the bypass and circulation regime. For $m > 0.5$ (Fig. 1, bypass regime), the gas slug bubble has a higher velocity as compared to the liquid slug ahead of it. This condition leads to the formation of a bypass regime (Fig. 6(a)), the liquid in the core of the tube forms the stagnation point at the nose of the slug bubble. The fluid elements (and hence the streamlines) around the tube core which are at the radius equivalent to the order slug radius deviate towards the annular film. The limiting case of such a condition is the slug bubble rising in the stagnant liquid inside the tube which leads to the formation of only one stagnation point at the bubble nose. On the other hand, for $m < 0.5$, the gas slug bubble has a lower in-situ velocity as compared to the velocity of the liquid slug ahead of it. This condition leads to the formation of a flow reversal feature in the liquid slug. Taylor (1961) proposed the presence of two stagnation points on the surface of the slug bubble for $m < 0.5$. The hypothesis from Taylor (1961) was confirmed by Cox (1964) during his experiments. The phenomenon of flow reversal could be explained intuitively by considering the velocities of the liquid slug and the terminal velocity of the gas slug in the tube. The intermittent liquid slug has a higher velocity than the in-situ gas velocity and a distinct flow reversal takes place around the central core of the tube (Fig. 6(a), circulation regime). The establishment of a flow profile with exactly $m = 0.5$ during the experiments is difficult, Cox (1964) acknowledged the finding of a flow profile with $m = 0.5$ more by chance than by design. The fluid only at the axis of the tube appeared strictly stationary for $m = 0.5$. The streamlines would deviate from the close vicinity of the slug stagnation point and the results would appear to be similar to the case of $m > 0.5$. The flow pattern inside the liquid slug (circulation or bypass regime) has repercussions on the overall mass transfer performance of the reactor.

The fluid elements remain in contact with the gas slug for longer time scales in circulation regimes due to the flow reversal behaviour. The shear stress profile over the wall of the reactor would also reverse periodically during the circulation regime leading to an even higher

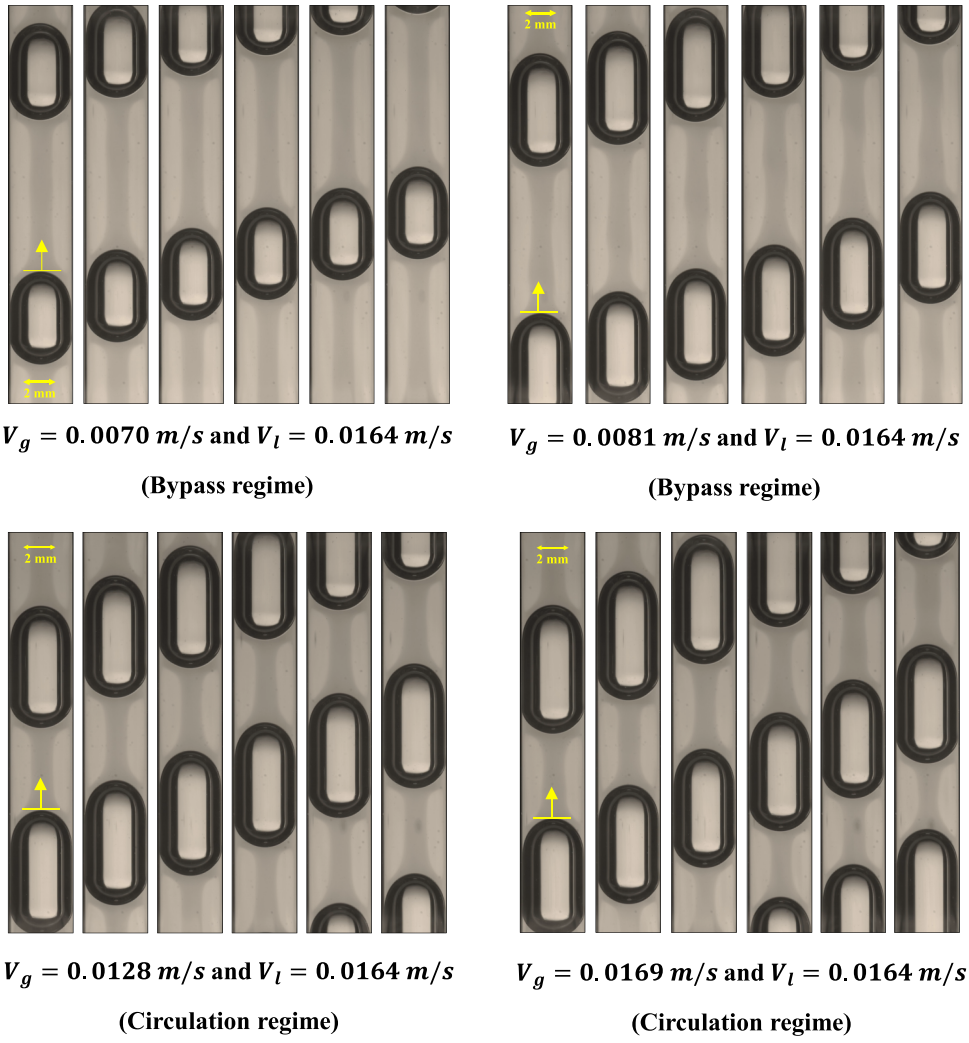

Fig. 7. Diffusion of Oxygen into the liquid slug between the bubbles at different superficial velocities. (a) Bypass regime for $V_g = 0.0070m/s$, (b) Bypass regime for $V_g = 0.0081m/s$, (c) Recirculation regime for $V_g = 0.0128m/s$ and (d) Recirculation regime for $V_g = 0.0169m/s$. Note the bypass regime and circulation regime at a constant liquid superficial velocity. Multimedia views have been added for two cases $V_g = 0.0070m/s$ and $V_g = 0.0128m/s$.

overall mass transfer coefficient. Operating the reactor under the circulation two-phase flow regime would be beneficial especially during hydrogenation reactions to convert unsaturated hydrocarbons to saturated states. The periodic reversal of the shear near the hydrogen-coated wall would bring the new fluid element into the wall contact. Fig. 7(a) and (b) show the bypass and recirculation regime (Fig. 7(c) and (d)) with the superficial velocity parameters from the experiments.

See the Multimedia views for bubble bypass Fig. 7(a) for $V_g = 0.0070m/s$ and recirculation regime Fig. 7(c) for $V_g = 0.0128m/s$ at a constant liquid superficial velocity. The time scales and length scale around the gas slug bubble and the liquid slug is of paramount importance in the prediction, quantification, and deducing operating characteristics of the gas absorber reactors. Abiev et al. (2019) proposed the three-layer model to quantify the mass transfer process in circular conduits. The three layers include the core region at the axis of the tube and bulk circulation flow. They slightly modified the criterion for the transition between the bypass and circulation regime. The nature of flow inside the conduit could be quantified in the form of liquid slug in-situ velocity-based Reynolds number, $Re_l = \rho_l U_l D_o/\mu_l$. The liquid Reynolds number, $Re_l < 150$, which suggests the laminar nature of the fluid inside the conduit. The assumption of the Poiseuille velocity profile seems feasible in the current experiments. Abiev et al. (2019) proposed parabolic Poiseuille laminar flow for proposing his transition criterion. They slightly modified the parameter, m proposed by Taylor (1961) as, $J = 2-(U_b/V_l)$, where V_l is the superficial velocity of the liquid and U_b is the bubble velocity. The modified transition criterion proposes, recirculation flow for $J < 0$ (Fig. 8(a)). Fig. 7 shows the flow pattern inside the circular tube at different gas superficial velocities, V_g and constant liquid superficial velocity, V_l. Consider the case with, $V_g = 0.0070m/s$ and $V_l = 0.0164m/s$ (Fig. 7) for which $J > 0$ (Fig. 8(a)), the fluid element from the annular film follows the spherical cap region of the gas slug towards the central axis of the tube. The presence of $J > 0$ causes the formation of only one stagnation point ahead of the gas bubble nose of the trailing bubble. The central stem (layer 1, Fig. 6(a), bypass regime) could be visualized between the two gas slugs which are around the single stagnation point of the trailing bubble. The lubrication fluid layer (layer 3, Fig. 6(a)) flowing downwards along the annular film of the gas slug could also be observed in the intermittent liquid slug. Only the central stem (layer 1) and lubrication fluid layer (layer 3) are present in the bypass regime. The Taylor vortex velocity, w_1 increases monotonically with the gas in-situ velocity with Re_l and w_1 are approximately three times the slug bubble in-situ velocity, U_b (Fig. 8(b)).

On the other hand, for $J < 0$, the reactor operates in the circulation regime (Fig. 6(a)). Consider the case with $V_g = 0.0169m/s$ and $V_l = 0.0164m/s$ (Fig. 7). The central stem connecting the two slug bubbles is thicker as compared to the central stem thickness in the bypass regime. A bulk Taylor vortex flow (layer 2) exists between the central core at the tube axis (layer 1) and the wall lubrication layer in the liquid slug (layer

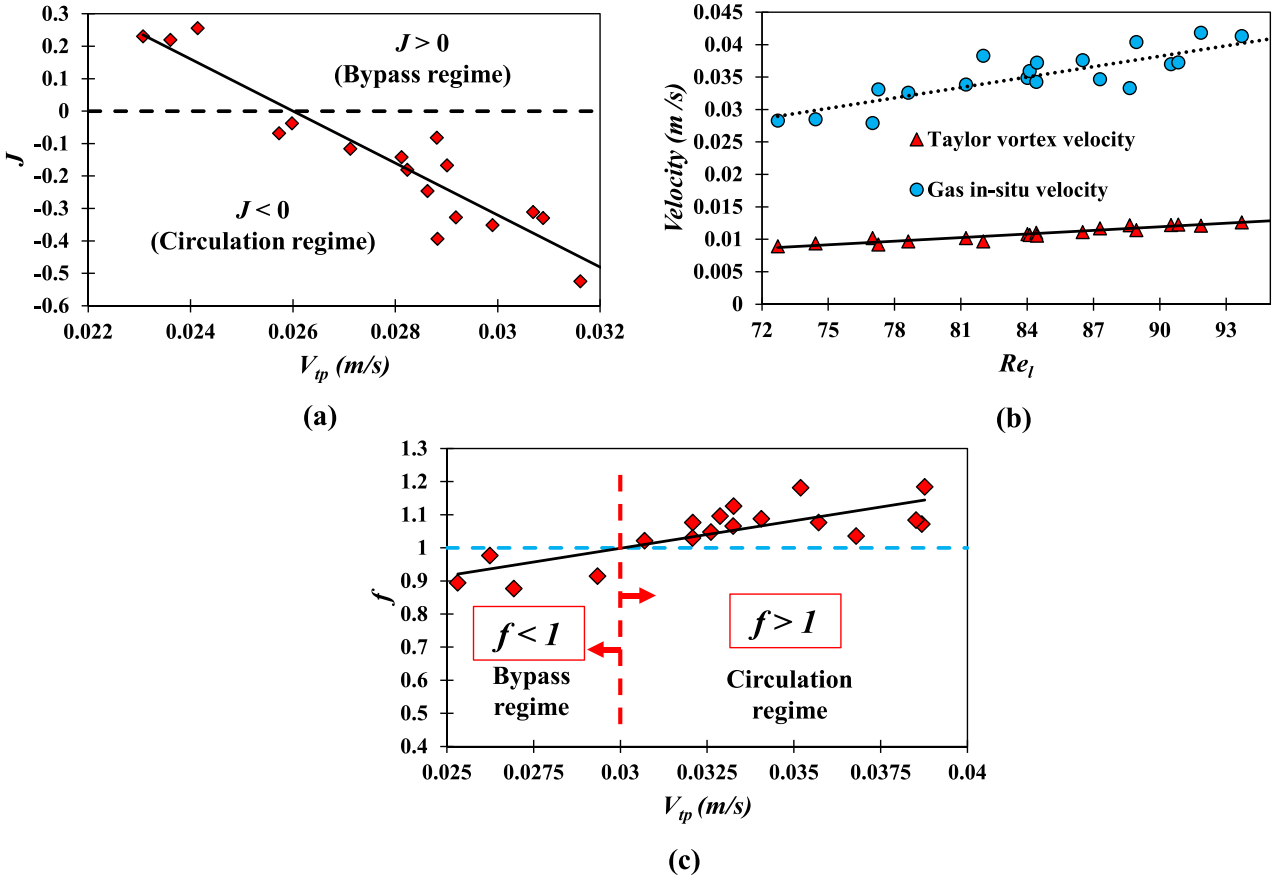

Fig. 8. (a) Variation of superficial two-phase flow velocity, U_{tp} (m/s) with the factor, J. Factor $J > 0$ represents the bypass regime and $J < 0$ represents the recirculation regime, (b) variation of circulation velocity, w_1 (m/s) and gas in-situ velocity with Re_l, (c) recirculation frequency, f in the liquid slug variation with the two-phase superficial velocity, V_{tp}.

3). The rotating bulk circulation flow (layer 2) in the form of a Taylor vortex is present only for $J < 0$. The Taylor vortex recirculation velocity could be deduced from a three-layer model originally proposed by Abiev et al. (2019) and further utilized by Butler et al. (2018). The Taylor vortex recirculation velocity, w_1 can be deduced from the Poiseuille velocity profile assumed in the liquid slug. The Poiseuille velocity profile, $u(x) = 2V_{tp}\left[1 - 4(x/D)^2\right] - U_b$, where U_b is the in-situ velocity of the gas slug measured by tracing the tip of the bubble nose across the high-speed video generated images in MATLAB. The eye of the vortex of characterised by $R_o = \left(R_1/\sqrt{2}\right)$,where $R_1 = (d/2)\sqrt{\{2 - (U_b/V_{tp})\}}$ is the point at which the velocity of the fluid element vanishes to zero. The recirculation velocity, $w_1 = 2\pi \int_0^{R_o} u(x)xdx$, is given by the integration of the Poiseuille velocity profile in the frame of reference relative the rising gas bubble with the in-situ velocity, U_b. Performing the integration eventually yields, $w_1 = \{V_{tp} - (U_b/2)\}$ by using value of R_o in the Taylor vortex (layer 2, circulation regime). The circulation velocity is the primary cause of transporting the gas from the Oxygen interface to the liquid slug. Fig. 8(b) shows the monotonic increase in the circulation velocity, w_1 (m/s) with the in-situ bubble velocity-based Reynolds number, Re_l. The bypass regime is observed for a very limited range of two-phase flow total superficial velocities. Generally, the bubble length, $L_b \sim 2D$, D is the channel diameter results in the bypass regime.

Furthermore, the recirculation frequency, f of the Taylor vortex is the major contributor of the heat and mass transfer enhancement in the tube. The recirculation frequency could be deduced from the velocity scale, $w_1 = \{V_{tp} - (U_b/2)\}$ over the length scale, $2L_l$. The recirculation frequency during the co-current slug flow becomes, $f = \{V_{tp} - (U_b/2)\}/2L_l$ (Butler et al., 2018). Implementing the model to the current experiment could be utilized to demarcate and differentiate the bubble bypass and circulation regime, respectively. The bubble bypass regime has low characteristic frequency, $f < 1$, while on the other hand, higher frequency of recirculation has been noted, $f > 1$ for circulation regime (Fig. 8(c)).

Fig. 9(a) shows a detailed view of the liquid slug during the recirculation regime. B1 and B2 are the tail of the leading bubble and the nose of the trailing bubble, whereas B3 represents the annular section of the slug bubbles. The liquid slug, S consists of the Taylor vortex with the subsections, S1 and S2 entrapped between the central stem and the wall lubrication layer. The annular films F1 and F3 are entrapped between the bubble interface and the wall, whereas F2 is the transient wall lubrication film in the liquid slug. Segment 1 (Fig. 9(a)) represents the diffusion from the bubble caps to the liquid slug. Segment 2 represents the diffusion between the layers of the slug S1 and S2 which form the Taylor vortex. Segment 3 represents the contribution from the leading bubble tail to the entrapped liquid slug. Segment 4 represents the diffusion between the transient film, F2, and outer layer S1 of the Taylor vortex. Segment 5 represents the diffusion from the bubble into the annular liquid film between the bubble interface and the tube wall. The saturated or unsaturated nature of this entrapped film has repercussions on the overall gas–liquid mass transfer coefficient. Segment 6 represents the diffusion between the layers of the central stem and the inner layer, S2 of the Taylor vortex. Segment 7 represents the convection between the annular film, F1, and the transition film, F2 of the liquid slug. The order of magnitude of the transition film, F2 is of the same order as the thickness of the annular film, F1. Fig. 9(b) shows the equivalent observations from the experiments at different gas superficial velocities.

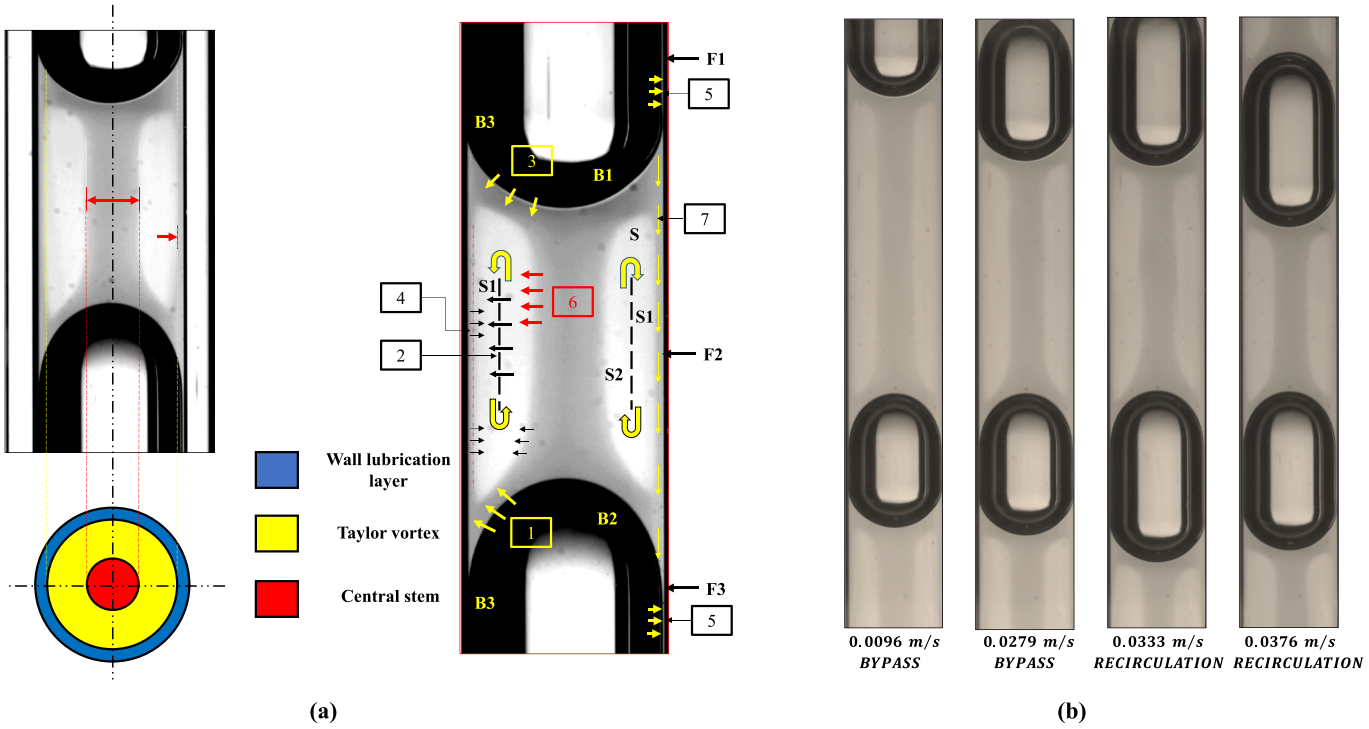

Fig. 9. (a) Structure of the liquid slug during the recirculation regime and (b) Flow pattern in the liquid slug at different gas superficial velocities, V_g and constant liquid superficial velocity, $V_l = 0.016m/s$.

3.3. Quantification for mass transfer in co-current gas–liquid slug flow

At this point, it is useful to analyse the nature of the flow regime which exists in the annular film around the bubble. The equation of continuity could be utilized to deduce the annular film velocity during the co-current flow (Eqs. (9) and (10)).

$$Q_l = Q_b + Q_f \tag{9}$$

$$U_{film} = \left|\left(Q_l - U_b A_b\right)/A_{film}\right| \tag{10}$$

Where, $Q_b = U_b A_b$ is the gas flow rate through the conduit due to the bubbles, $Q_l = U_l A_l$ is the liquid superficial velocity, A_b is the cross-section area of the bubble and A_{film} is the cross-section area of the annular film. The film Reynolds number, $Re_{film} = \left(U_{film}\delta_{film}\rho_l\right)/\mu_l$ (Fig. 10), for the current study ranges from 5.7 to 15.4 which suggests the presence of the laminar flow condition. The liquid film velocity may be high, but the Reynolds number remains small due to the length scale of the annular film, $\delta_{film} = 0.0143 - 0.0183mm$. The annular film velocity, $U_{film} = 0.77 - 1.28m/s$ for the total superficial velocity, $V_{tp} = 0.025 - 0.038m/s$. Oxygen diffuses from the slug bubble to the falling annular film, having the length, $L_b - d_b$ (where, d_b is the slug bubble diameter). Fourier number, $Fo = D_{O_2} t_{film}/\delta_{film}{}^2$ is used as the criterion for deciding the level of saturation in the annular film around the slug bubble.

Fourier number in the ratio of the diffusive rate of transport to the storage rate in the concentration boundary layer. The time scale, $t_{film} = (L_b - d_b)/U_b$ (inset Fig. 10(a)), is the duration for which the fluid element remains in contact with the annular film of the slug bubble. The mechanism of mass transfer in the annular film is dominated by convection. Abiev (2020) recently suggested that the annular film is not

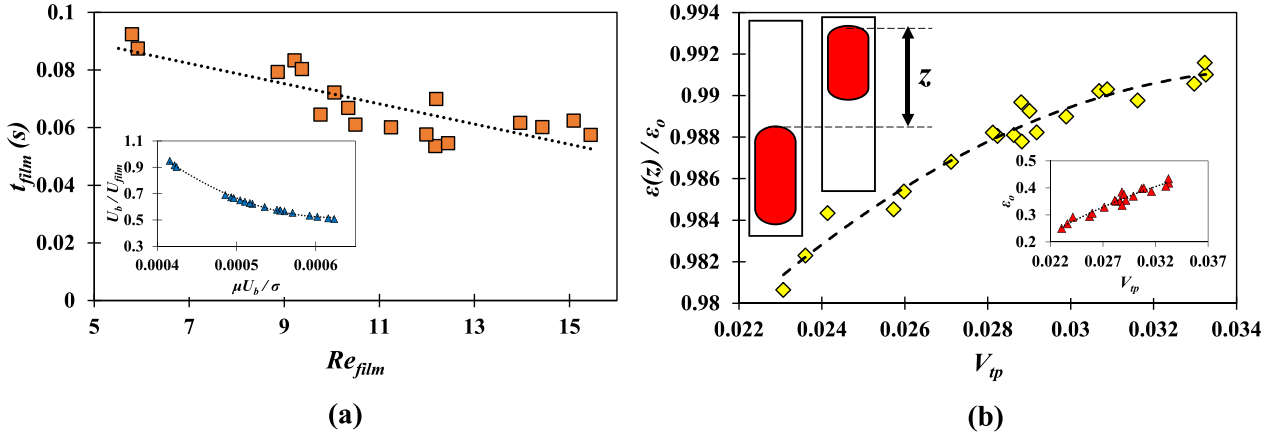

Fig. 10. (a) Variation of the fluid element residence time, t_{film} with the film Reynolds number, $Re_{film} = \left(U_{film}\delta_{film}\rho_l\right)/\mu_l$. The inset figure shows the variation in the ratio of in-situ slug velocity and annular film velocity, U_b/U_{film} with the capillary number, $Ca = \mu U_b/\sigma$. (b) Variation of the void fraction ratio, $\varepsilon(z)/\varepsilon_o$ with the total superficial velocity, V_{tp}. The inset figure shows the variation of the initial void fraction, ε_o with V_{tp}.

saturated due to the short contact time scale if $Fo < 0.1$. In the current investigation the Fourier number, Fo 0.0045 −0.0027, suggests that the penetration theory-based mass transfer models are appropriate to estimate the overall mass transfer coefficient.

Abiev (2020) suggested that the annular film is not saturated due to the short contact time scale if $Fo < 0.1$. The penetration theory could be deployed to quantify the liquid side mass transfer coefficient, neglecting the convective terms gives the temporal evolution of the concentration of the solute in the liquid element as, $\partial c/\partial \tau = D_{O_2}\left(\partial^2 c/\partial z^2\right)$, where D_{O_2} is the diffusivity of the Oxygen from the gas to the liquid and z is the normal direction to the gas–liquid interface ($z = 0$). The solution of the unsteady discussion equation is in the form of the error function, the mass flux of Oxygen, $N_{O_2} \; -\rho(\partial c/\partial \tau)_{z=0}$ if the concentration $c_{O_{2,i}}$ 0 at the gas–liquid interface. Introducing the mass flux, $N_{O_2} = \; -\rho(\partial c/\partial \tau)_{z=0}$ into the error function based solution of the diffusion equation yields, $N_{O_2}(\tau) = \rho\sqrt{D_{O_2}/\pi\tau}\left(c_{O_{2,i}} - c_{O_{2,b}}\right)$, where, $c_{O_{2,b}}$ is the concentration of the Oxygen in the bulk far away from the gas–liquid interface. The liquid side mass transfer coefficient, $k_l(t) = \sqrt{D_{O_2}/\pi\tau}$ could be deduced from the above expression for the mass flux of Oxygen into the liquid. The expression, $k_l(\tau) = \sqrt{D_{O_2}/\pi\tau}$ could be integrated for the time interval, $\tau = t_{film}$ for which the fluid molecule remains in contact with the gas–liquid interface would yield, $k_{l,avg} = \frac{1}{t_{film}}\int_0^{t_{film}} k_l(\tau)d\tau$, which could be further simplified as, $k_l = 2\sqrt{D_{O_2}/\pi t_{film}}$. Vandu et al. (2005) used $k_l = 2\sqrt{D_{O_2}/\pi t_{film}}$ for deriving the expression for $k_l a$, where a is the interfacial area per unit volume (m^2/m^3). The specific surface area, a has been deduced from the experiments by using the in-house developed MATLAB code which deploys the in-built functions, boundaryFacets and alphaShape (Fig. 3).

Recently, Abiev (2020) provided an algorithm for predicting the mass transfer coefficient based on the hydrodynamic parameters as input. A mass transfer correlation for a short contact time scale in the annular film is appropriate for the quantification of the current experimental study. Vandu et al. (2005) provided the expression for $k_l a$ (s^{-1}) for co-current two-phase flow in a 3 mm diameter capillary based upon the penetration theory model. The penetration theory model assumes the physical transport of the fluid element sliding over the gas–liquid interface. The replenishment of the fluid element over the gas–liquid interface ensures a high mass transfer coefficient. Combining the mass transfer coefficient, k_l (m/s) and interfacial area per unit volume, a (m^2/m^3) is followed as a convention because the interfacial area, a is generally difficult to quantify during the reactor design. The overall gas–liquid mass transfer coefficient, $\left(k_{gl}a_{gl}\right)_{overall}$ in the absence of gas–solid mass transfer could be modelled by Eq. (11).

$$\left(k_{gl}a_{gl}\right)_{overall} = \left(k_{gl}a_{cap}\right)_{cap} + \left(k_{gl}a_{film}\right)_{film} \tag{11}$$

Where, $\left(k_{gl}a_{cap}\right)_{cap}$ is the contribution of the hemispherical caps of the slug bubble and $\left(k_{gl}a_{film}\right)_{film}$ is the contribution from the annular film of the slug bubble to the overall mass transfer coefficient. The overall mass transfer coefficient, $\left(k_{gl}a_{gl}\right)_{overall}$ would be simply referred as $k_l a$ during further discussion. The expression for $k_l a$ based upon the two-film model has been proposed by Vandu et al. (2005), refer to Eq. (12).

$$k_l a = \underbrace{\frac{2\sqrt{2}}{\pi}\sqrt{\frac{D_{O_2}U_b}{D}}\left\{\frac{4}{L_{uc}}\right\}}_{Cap\ contribution} + \underbrace{2\sqrt{\frac{D_{O_2}U_b}{\varepsilon_o L_{uc}}}\left\{\frac{4\varepsilon_o}{D}\right\}}_{Annular\ film\ contribution} \tag{12}$$

The mass transfer coefficient, $k_l a$ consists of the contribution from the bubble caps and annular film contribution, which are highlighted as a term first and second in Eq. (12). The proposed model has provided a good agreement with the experimental observations (Vandu et al. (2005)). The correlation proposed by Vandu et al. (2005) could be implemented for the current investigation and an approximation for the liquid side mass transfer coefficient, $k_l a$. Fig. 11(a) shows the monotonic increase in the mass transfer coefficient, $k_l a$ with the two-phase flow superficial velocity, V_{tp}. The monotonic increment in $k_l a$ is expected at such low two-phase flow superficial velocity, similar results have been reported in the review paper by Haase et al. (2016). Fig. 11(b) shows the individual contribution of the slug bubble cap and the annular film with the two-phase flow superficial velocity. The contribution of the cap to the value of $k_l a$ is lower as compared to the film contribution.

The shrinkage of the bubble during the gas–liquid mass transfer process is always a design consideration for designing film flow reactors. The shrinkage of the bubble into the confined channel would eventually affect the acceleration pressure drop and its repercussions would be observed in the change in the overall pressure drop fluctuations. Therefore, an estimate of the bubble shrinking is of paramount importance. The transfer of the gas to the liquid would continue until the surrounding liquid saturates completely ($C^* \sim 0.009 kg/m^3$). The balance between the mass flux from the bubble to the surrounding liquid would increase the concentration of the gas in the liquid. The shrinkage of the bubble in the channel reduces the gas void fraction, ε_o. Recently, Butler et al. (2018) and Abiev (2020) estimated the bubble shrinkage by balancing convective mass flux from the bubble interface to the increase in the dissolved gas concentration in the surrounding liquid (Eq. (13).

$$\varepsilon(z)/\varepsilon_o = \left[1 - (1-\varepsilon_o)exp\left\{\frac{C^*}{\rho_g}\left(1 - exp\left(\left(-k_l a\right)z/U_{tp}\right)\right)\right\}\right]\Big/\varepsilon_o \tag{13}$$

Where, $\varepsilon(z)$ is the gas void fraction, ΔV is the elementary volume at the distance z from the origin where the initial void fraction is ε_o. $C(z)$ is the concentration profile of the dissolved gas in the surrounding liquid. For the current investigation, the ratio of gas void fraction, $\varepsilon(z)$ at $z =$

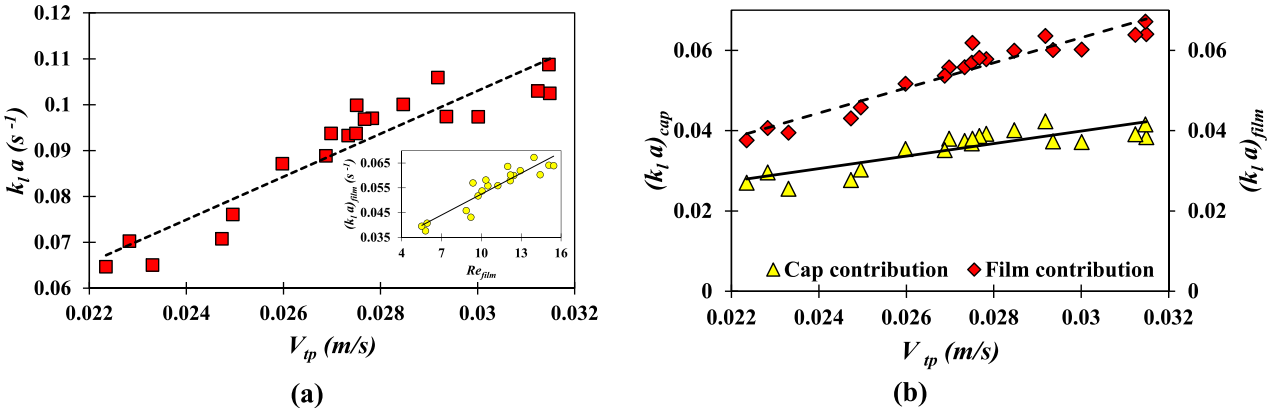

Fig. 11. (a) Variation of liquid side mass transfer coefficient, $k_l a$ (s^{-1}) with V_{tp}, inset figure shows the variation of film Reynolds number with the film contribution to the mass transfer coefficient, (b) variation of $(k_l a)_{cap}$ and $(k_l a)_{film}$ with two-phase superficial velocity, V_{tp} (m/s).

500*mm*, to the initial void fraction, ε_o ranges from, $0.98 < \varepsilon(z)/\varepsilon_o < 0.99$ (Fig. 10(b)), therefore, the acceleration pressure drop could be neglected while designing the hydrodynamics reactor with the similar dimensions. Increasing the two-phase total superficial velocity, $V_{tp} = V_l + V_b$ provides less time for the oxygen slug bubble to diffuse into the surrounding liquid therefore, $\varepsilon(z)/\varepsilon_o$ increases.

3.4. Estimation of the concentration profile in the liquid slug

The high convective flux over the bubble interface flushes the dissolved oxygen in the liquid to the entrapped liquid slug. Fig. 12 ((a) to (d)) shows the normalized concentration, C/C_{max} with the normalized radial location, x/D, where C_{max} is the maximum concentration in the liquid slug. Section AA is at the tip of the slug bubble and section BB is present in the middle of the liquid slug.

The fitted polynomial of the concentration profile (Eq. (14) reflected the three-layer flow structure along with the wall friction film. The parameters of the fitted curve for section AA and section BB have been presented in Tables 3 and 4 respectively. The data from section AA and Section BB represent the concentration at bubble nose and liquid slug center, respectively. Both section AA and BB show the maxima at the center of the tube which is expected due to the flow pattern developed between the slug bubbles. Section AA profile is having platykurtic nature (as compared to the section BB) along the bubble nose due to dissolution of the oxygen along the hemispherical cap. The slug bubble nose deviates streamline away from the tube center with the fluid elements having the maximum velocity at gas–liquid interface. Similarly, section BB is also having the same shape, but the maxima is having positive kurtosis along the tube center. The maxima at section BB are due to the presence of the central stem from the three-layer structure. Near the wall, both section AA and BB show a slight increment due to the presence of the wall lubrication layer or Taylor vortex in the liquid slug. The polynomial functional form ensured the capturing of the Taylor vortex radius, R_o and the increment in the concentration near the wall

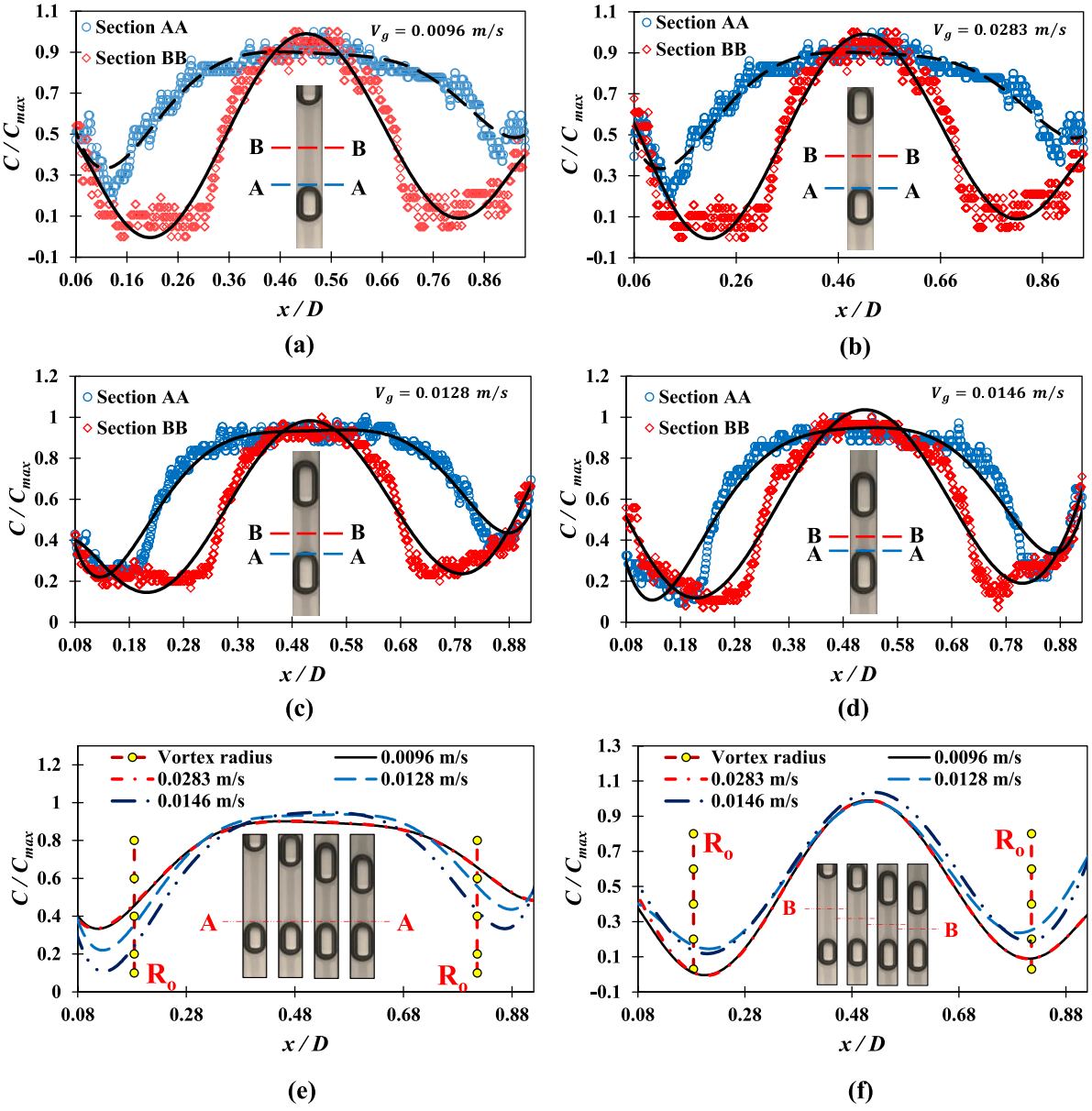

Fig. 12. Concentration ratio, C/C_{max} at the different radial locations, x/D, (a) $V_g = 0.096m/s$ and $V_l = 0.016m/s$, (b) $V_g = 0.0283m/s$ and $V_l = 0.016m/s$, (c) $V_g = 0.0128m/s$ and $V_l = 0.016m/s$, (d) $V_g = 0.0146m/s$ and $V_l = 0.016m/s$, (e) fitted curve for the concentration profile at the top of the bubble nose with the location of the center of the Taylor vortex, R_o and (f) concentration profile at the center of the liquid slug.

Table 3
Parameters of the concentration profile, C/C_{max} at section at the bubble nose.

$V_g(m/s)$	a	b	c	d	e	f	g
0.0096	226.76	−721.3	901.23	−557.71	173.22	−22.77	1.36
0.0283	199.65	−634.34	791.95	−489.79	151.64	−19.54	1.19
0.0128	432.72	−1322	1590.1	−952	289.85	38.82	2.05
0.0146	466.03	−1406.5	1680.3	−1007.1	309.53	−42.03	2.12

Table 4
Parameters of the concentration profile, C/C_{max} at the section in the liquid slug.

$V_g(m/s)$	a	b	c	d	e	f	g
0.0096	−394.76	1194.4	−1320.6	636.85	121.31	5.25	0.45
0.0283	−387.17	1165.1	−1275.4	601.64	106.81	2.30	0.68
0.0128	−400.53	1238.6	−1416.1	728.99	163.88	13.58	0.04
0.0146	−272.65	866.72	−989.47	481.09	86.62	1.68	0.72

lubrication layer.

$$(C/C_{max}) = a(x/D)^6 + b(x/D)^5 + c(x/D)^4 + d(x/D)^3 + e(x/D)^2 + f(x/D) + g \quad (14)$$

Prediction of the dissolved Oxygen concentration very near the wall ($x/D < 0.05$) is difficult due to the presence of the tube wall curvature, nevertheless, the proposed polynomial profile predicts the increment in the dissolved oxygen concentration which matches the physical observations. The polynomials derived from the concentration plots could be indispensable for the validation of the commensurate numerical simulations. Butler et al. (2018) reported similar observations around the location of the Taylor vortex in their PLIF-I-based experimental investigation technique. Refer to Fig. 12(e), the increase in the gas superficial velocity, $V_g = 0.0146m/s$ resulted in a sharp change in the concentration profile towards the wall lubrication layer. The presence of the stagnation ring could be observed around the center of the tube with the plateau shape of the concentration profile near the bubble nose (Kreutzer et al., 2005; Taylor., 1961; Cox, 1964). The plateau in the concentration at the top of the bubble nose is due to the accumulation of oxygen. The concentration of the dissolved oxygen further reduces from the bubble nose towards the tube wall. The stagnation zone extends until, x/D 0.02 around the bubble nose and the transient wall lubrication film in the liquid slug contributes to an increment in the dissolved Oxygen concentration near the tube wall (Fig. 9(a), film F2). Refer to Fig. 12(f), increasing the gas superficial velocity to, $V_g \sim 0.0146m/s$ increased the concentration of the dissolved Oxygen in the central stem. The increment with the superficial velocity is expected due to the increase in the surface area of the bubble which provides more residence time between the fluid and the gas.

The colorimetric technique provides the correct flow structure in the liquid slug as shown by the validation obtained from the three-layer model. However, the resulting concentration in the liquid slug has to be studied continuously with a sensor based upon the fluorescence quenching technique or simultaneous PLIF system-based measurement.

4. Conclusion

Co-current flow slug train has been established by using an Oxygen sensitive dye solution and pure Oxygen gas in a millimetric channel. The slug bubble sheds the pink color during its traversal through the dye solution which is captured by a high-speed camera along with the bubble hydrodynamics. In-house developed image processing codes have been used to calibrate the dissolved oxygen concentration in the liquid slug. Two different regimes have been predicted by using the gas in-situ gas velocity and liquid slug superficial velocity base parameter, $J = 2 - (U_b/V_l)$. The slug bubble has only a single stagnation point for $J > 0$ (bypass regime) and two stagnation points for $J < 0$ (recirculation regime). Bubble in-situ velocity-based Reynolds number, $Re_l < 77$ resulted in the bypass regime, while, on the other hand, $77 < Re_l < 96$ resulted in the recirculation regime. The bubble recirculation regime results in the formation of the three-layer structure in the liquid slug. The first layer consists of the central stem around the axis of the tube and the nose of the slug bubble. The wall lubrication layer consists of the transient liquid film in the liquid slug (third layer). A recirculation Taylor vortex (second layer) is entrapped between the central stem and the wall lubrication layer. A short contact time ($Fo = 0.036 - 0.063$) has been observed during the co-current flow. Penetration theory-based semi-analytical correlation has been used to quantify the mass transfer along with the dye-based visualization. Radial concentration profiles have been estimated by using the implementation of the calibration curve. The colorimetric technique is beneficial in visualizing the mass transfer performance of the channel in the resource-limited setting as compared to the expensive laser-based investigations.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix 1:. Principle of colorimetric technique

The colorimetric technique is based on the use of an oxygen-sensitive dye. There are some chemical compounds available, when they are subjected to oxidation or reduction reaction then either intense color appears in the oxidized form, or no color or conjugate (opposite) color appears in the reduced state (Kherbeche et al. 2013). Resazurin dye is one of the chemicals which provide the pre-requisite condition for the colorimetric reaction (Dietrich et al., 2013; Yang et al. 2017; Xu et al. 2020; Reichmann et al. 2021; Mei et al. 2022; Hirano et al., 2022).

The reaction is catalyzed by glucose and Sodium hydroxide. The glucose present in the solution reacts with OH^- ions from NaOH to form the D-Gluconic acid by the following oxidation reaction as Eq. (A1).

$$\underbrace{HOCH_2(CHOH)_4CHO}_{(Dextrose)} + 3OH^- \rightarrow \underbrace{HOCH_2(CHOH)_4CO_2}_{(Gluconic\ acid)} + 2H_2O + 2e^- \quad (A1)$$

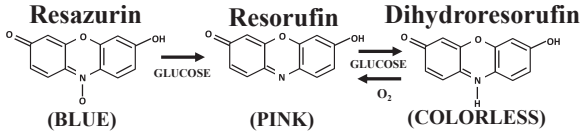
The generation of the pink color from the oxygen bubble results from the reversible reaction between resorufin (pink) and dihydroresorufin (colorless).

$$\underbrace{O_2 + 2.Dihydroresorufin \rightarrow 2.Resorufin + 2.H_2O}_{(Fast\ reaction)} \quad (A2)$$

$$\underbrace{Resorufin + Dextrose \rightarrow Dihydroresorufin + Gluconicacid}_{(Slow\ reaction)} \quad (A3)$$

The conversion of dyhydroresorufin (colorless) to resorufin (pink) is faster as compared to the convective time scale of the bubbles (Eq. (A2) and (A3) respectively). This is an important feature of the resazurin that can be used as a tool for visualizing the mass transfer around a Taylor bubble. The equivalent concentration of Oxygen (mg/L) could be calculated back with the help of the stoichiometry from the above reactions with the help of Eq. (A4). From stoichiometry, one mole of dyhydroresorufin reacts with two moles of oxygen. Similarly, one mole of resazurin reacts to produce one mole of dihydroresorufin (Eq. (A4)). The concentration of the dissolved oxygen around the bubble could be back-calculated. The whole reaction scheme can be represented as Eq. (A5).

$$n_{O_2,transfered} = n_{O_2,reacted} = n_{resazurin}/2 \quad (A4)$$



(A5)

The oxygen-sensitive dye resazurin reacts with Oxygen in the presence of sodium hydroxide and glucose results a colorless solution of dihydroresorufin (B). If it reacts in the presence of oxygen, then it is characterized by an intense pink color solution of resorufin (C) (Eqs. (A1)-(A3) and Eq. (A5)). The extent of the oxidation reaction and the amount of transferred (or dissolved) oxygen, are directly proportional to the color intensity (grey value), for a given concentration of resazurin (Dietrich and Hebard, 2018; Zhao et al. 2021). The pink color from the bubble should remain for a sufficient time in the surrounding fluid for proper visualization. Conversion of dihydroresorufin (B) back to colorless resorufin (C) is a slow reaction which makes the mass transfer visualization possible by the high-speed camera. An optimal composition of the Sodium hydroxide and glucose solution should be determined to control the conversion of the pink color back to the colorless fluid. It results from a balance between the reaction kinetic rates and the requirement in terms of adequate color intensity levels. Zhang et al. (2014) studied the kinetics of this reaction and reported that the reaction between dihydroresorufin (B) and oxygen (O_2) is of order 2 with respect to the oxygen and dihydroresorufin. The same order of reaction was also utilized by Yang et al. (2017) in explaining the kinetics of the reaction. One may refer to Yang et al. (2017) for further details on the chemical kinetics of the reaction. The section 3.1 summarizes the image analysis to identify the pink color shedding regions from the bubble by a monochromatic high-speed camera.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ces.2023.119388.

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Experimental investigations of the production of methyl acetate in batch catalytic distillation process in the presence of Indion 180

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As a novel study, esterification of acetic acid with methanol has been studied in a simple batch reactive distillation apparatus to produce methyl acetate as main product and water as byproduct. Novel solid catalyst named Indion 180 has been used in this esterification process. The product methyl acetate can be distilled out in two ways namely sequential and simultaneous reactive distillation. In the simple distillation batch process, first the reaction is carried out till the equilibrium with total reflux of vapours, and then distillation is carried out where the vapours are condensed and collected separately with zero reflux. In the second case, simultaneous reaction and distillation processes are carried out. During these experiments, the dynamics of bubble point temperature of the reboiler is recorded and analyzed. From the experimental results it is found that the maximum purity of methyl acetate in instantaneous distillate of reaction followed by distillation and simultaneous reaction and distillation are 0.847 and 0.782, respectively, as analyzed by gas chromatography. From these studies it is found that a batch distillation apparatus itself can be used in certain way to produce the desired product for the case of methyl acetate production by monitoring the temperature regime of the reboiler.

Keywords: Dynamics, Esterification, Ion-Exchange Resin, Reactive Distillation

Methyl acetate is produced from a reaction between acetic acid and methanol as follows.

$$CH_3COOH + CH_3OH \rightleftharpoons CH_3COOCH_3 + H_2O \quad \ldots (1)$$

Without catalyst, the liquid state reaction is very slow [1]. But with catalyst such as Amberlyst or Indion ion exchange resins, the reaction rate increases [1-7]. The reaction rate increases but it is a reversible reaction therefore conversion reaches a constant value after some reaction time. The reaction rate data shows a substantial dependence on catalyst loading and temperature of the reaction mixture. Hence the catalytic reaction kinetics is to be understood in depth in order to obtain high conversion of the reactants in manufacturing [8-11].

The esterification kinetics between acetic acid and methanol was studied in presence of Amberlyst 36 solid resin catalyst by Mekala *et al.* [12]. The effect of temperature, mole ratio, catalyst loading, catalyst particle size and agitation speed on the acetic acid conversion were studied in a batch reactor. Mekala & Goli studied the production of methyl acetate in a packed bed reactive distillation column[13], where the column has 3 meter height and 50 mm diameter. The effect of reboiler temperature, feed flow rates, reflux ratio on the conversion of acetic acid and methyl acetate purity were also studied. A general framework for the dynamic simulation and optimization of global batch synthesis has been developed by Elgue *et al.*[14]. The authors discussed the application of global batch synthesis to the optimization of a methyl acetate production process[14]. Experiments performed on a batch pilot plant allow validating the dynamic model. Hence, optimal tuning of the operating parameters of the reactive batch distillation was investigated by means of the dynamic optimization procedure.

In another report[15], the authors performed the simulations for synthesis of methyl decanoate in a semi batch reactive distillation. Two batch distillation columns namely SBD and i-SBD are considered. They observed that the energy savings is more in i-SBD compared to SBD. The capital savings is 36.61%. The production and purification of levulinic acid was studied in a continuous reactive distillation[16]. Various alternative designs performed for reactive distillation. They found that from their designs 23% reduction in cost of equipment and 24% in energy consumption when compared to conventional process. The esterification of oleic acid with glycerol performed in presence of low cost and efficient Indion

catalyst by Diana *et al.* [17]. The catalyst performance was studied for different temperatures, catalyst loading and mole ratios. At optimal conditions an acid conversion was reported as 78%.

Industrially, the product of interest that is, methyl acetate should be separated in as pure form as possible. Reaction as shown in Eq. (1) tells that when the reaction proceeds, there would be a total of four components in the reaction mixture that is acetic acid, methanol, methyl acetate and water. Now, the manufacture of methyl acetate could be done in two different methods broadly: (i) Distillation after the reaction going to equilibrium and (ii) simultaneous distillation while the reaction is proceeding. Again there could be variation of each of these methods i.e., batch[14], semi batch[15] and continuous (column) reactive distillation[16] or the distillation followed by reaction.

Feasibility of separation by distillation should be assessed primarily from boiling points and vapour liquid equilibrium (VLE) diagrams. The boiling points of the components here are 56°C (methyl acetate), 65°C (methanol), 100°C (water) and 118°C (acetic acid). The molecular weights are 74 g/mol, 32g/mol, 18 g/mol and 60 g/mol, respectively. There is good possibility that the main product methyl acetate could be selectively distilled since the boiling point of it is the lowest of all the four components. But, the purity and recoverability of methyl acetate in distillate is affected by azoetrope formation and multi component VLE. The methyl acetate/methanol azeotropic composition is 81.3 wt% methyl acetate and 18.7wt% methanol.

Till now there are no studies available in the literature for the production of methyl acetate using simple distillation mode. In this paper, the experimental kinetics of multi-component distillation and simultaneous reactive distillation are presented for a batch process using simple distillation apparatus. The reaction is conducted at constant temperature till the equilibrium and the simple distillation is used to separate the components. In the second experiment the reaction and distillation are conducted in a simple batch distillation process. The interesting facts about the temporal variations of the composition of the distillate and residue are presented for the reactive batch distillation process.

Experimental Section

Chemicals

Methanol (purity=99% w/w) and Acetic acid (purity=99.95%w/w), supplied by SD Fine Chemicals Ltd. (Mumbai, India), were used in the present study. The solid acid catalyst, Indion 180, used for the esterification reaction was supplied by Ion-Exchange India Limited, Mumbai. Indion 180 has cross-linked three-dimensional structures of polymeric material, obtained by sulfonation of a copolymer of polystyrene and divinyl benzene (DVB). It is an opaque and dark grey colored solid spherical bead. The physical property of this catalyst is given in our earlier publication[6,11].

Experimental setup

The schematic diagram of a batch distillation apparatus used for conducting the experiments is shown in Fig. 1. It consists of a round bottom flask placed in a rota mantle with facility for magnetic stirring, electrical heating and temperature measurement by PT-100 thermocouple connected to a digital display with 0.1°C resolution. There is a horizontal condenser connected to the top port of the reboiler flask. Water at room temperature is used as coolant (25°C). A collection vessel is provided for collecting the distillate.

Experimental procedure

The experiments were conducted in presence of the Indion 180 a novel catalyst in a batch reactive distillation in a simple distillation apparatus. Reactive distillation was carried out to produce methyl acetate from acetic acid and methanol using Indion 180 as a solid ion-exchange resin catalyst in a simple distillation apparatus as shown in Fig. 1. Unlike the reboiler-column combination, a simple distillation apparatus was used to conduct reactive distillation

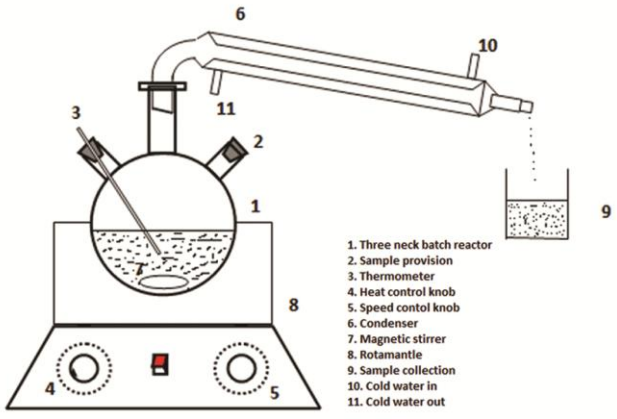

Fig. 1 — Schematic diagram of the batch distillation apparatus

where the vapours were condensed and collected as the catalytic reaction proceeds in the reboiler flask. The aim was to quantitatively measure the distillate or product purity in terms of the methyl acetate's mole fraction in it. The composition of instantaneous distillate, cumulative distillate and that of the reactant mixture in reboiler are monitored. Such data provided a very interesting experimental kinetics of simultaneous reactive distillation. In these experiments; the heat was supplied at an appropriate rate in order to maintain constant drop by drop condensation of distillate. The temperature of the mixture in round bottom flak was noted as a function of the time with the help of a thermocouple and digital indicator. The distillate and boiler flask samples were collected at various times or temperatures and analyzed using Gas Chromatography (GC) to determine the concentration of each of the four components.

Reaction followed by Distillation

The esterification reaction was carried out by taking 2.5 mol of pure acetic acid and 2.5 mol of methanol and catalyst (Indion 180) at loading of 0.025 g/cm^3 of the reaction mixture. Initially the reaction mixture was heated to 60°C and the catalyst was added. Based on a detailed kinetic study it was found that the conversion of the reactants goes to equilibrium within 3 h of time. The temperature is maintained at 60°C by controlling the heater in on/off mode. At end of 3 h, the reaction mixture was filtered to separate the catalyst particles. Now the resultant liquid mixture contains both the products (methyl acetate and water) and un-reacted reactants (acetic acid and methanol). This mixture is subjected to simple distillation. The second experiment was conducted at the same temperature of 60°C to study the reaction kinetics.

Simultaneous RD in simple distillation apparatus

The experiment was started by taking equal number of moles (2.5 mol each) of acetic acid and methanol and charging them to the round bottom flask. Immediately, catalyst particles were added to the reactant mixture with a pre-calculated catalyst loading of 0.025 g/cm^3. The glass flask or the reboiler was heated by supplying heat through an electric heater placed in the rota mantle, which surrounds the flask up to halfway of its volume. The liquid level in the flak was maintained below height of electrical heating coil to get the uniform heat supply to the reactor. Simultaneously the magnetic stirrer was switched on to maintain an rpm of 240 for the magnetic stirrer. These operating conditions ensured uniform heating and availability of catalyst in the reactant mixture. Simultaneously the distillate was obtained and analyzed for methyl acetate concentration with GC. The experiment was repeated at the same conditions as mentioned above to find the deviation of the experimental data.

Analysis

The samples were analyzed using gas chromatography (GC-2014 ATF, Schimadju, Japan.) equipped with a thermal conductivity detector. Porapak-Q (2 m length and 3.17 mm id) packed column was used to analyze the sample. High purity hydrogen gas was used as a carrier gas at a flow rate of 30.0 mL/min. The oven temperature was programmed at 323.15 K for 1 min and then raised from an initial value of 323.15 K to 443.15 K at a ramp rate of 10 K/min and was held at 443.15 K for 2 min. The detector temperature was maintained at 473.15 K.

Results and Discussion

Reaction followed by distillation

The heating during simple distillation was maintained and adjusted such that there was only a drop by drop condensation of distillate. The time taken for every 10°C raise in the temperature of the residue mixture was noted and it is represented graphically in Fig. 2. The initial mixture was at room temperature of about 25°C. As it was heated, the temperature increased up to 55°C and condensation started. During condensation the temperature seems to rise slowly. This is the regime II where methyl acetate gets distillates majorly. After, some more heating, there is a steeper increase in temperature. This is

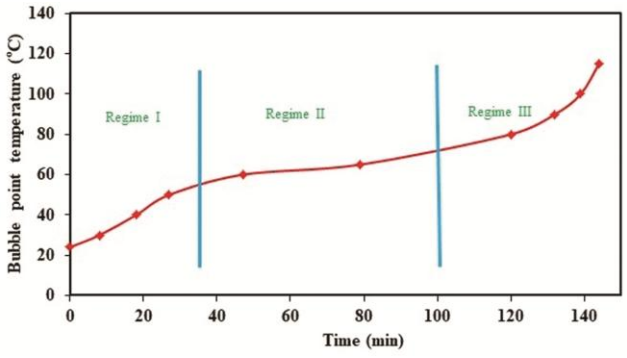

Fig. 2 — Residue's bubble point temperature versus time for case of reaction followed by distillation

because the high boiling components would be in higher fraction in the residue.

The composition of the residue as a function of time is recorded and represented in Fig. 3. The instantaneous composition of the distillate is represented in Fig. 4. Both these graphs give us a complete picture of the dynamics of distillation separation technique under quasi-equilibrium condition. These graphs are useful industrially to decide upon first cut as zone II. That is to say that the distillate collected between 55℃ and 80℃ offers higher purity of Methyl acetate. Beyond 80℃ of the residue temperature, the concentration of methyl acetate would be very low. For further purification a second and third sequential simple distillation could be conducted.

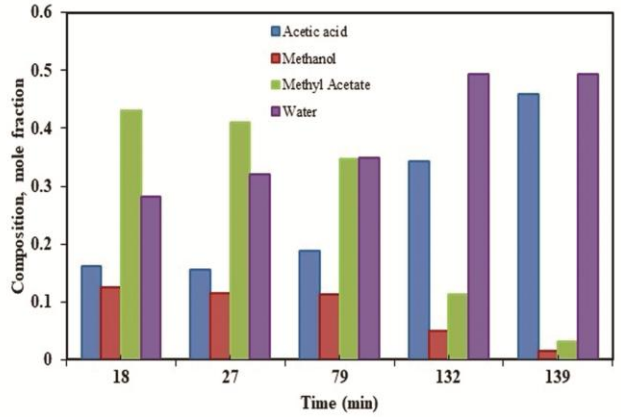

Fig. 3 — Composition of residue for the case of reaction followed by distillation

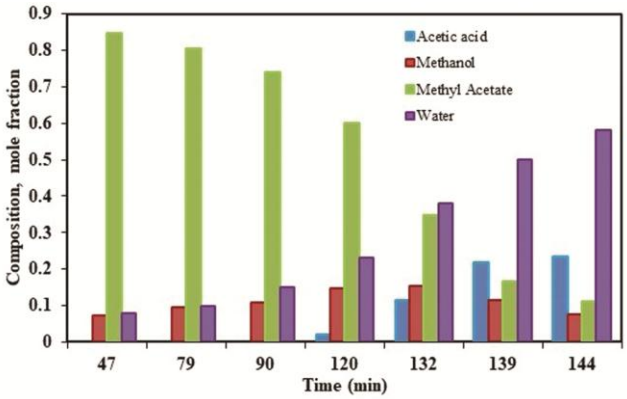

Fig. 4 — Composition of instantaneous distillate for the case of reaction followed by distillation

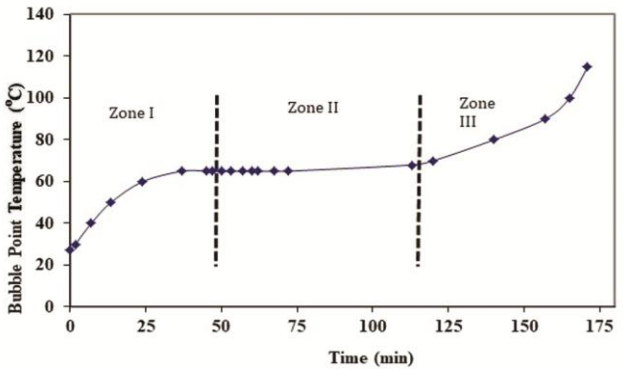

Fig. 5 — Residue's bubble point temperature versus time for simultaneous reaction and distillation

Simultaneous reaction and distillation

The resultant temperature variation of the residue in the flask is plotted against the time as shown in the Fig. 5. The temperature raised in the first zone and constant in the second zone. In the third zone suddenly the temperature raised to availability of high boiling acetic acid which comes lastly. Low boiling components have come first at low temperature; hence the temperature rose in the first zone, where as in the second zone the mixture of low and high boiling components separates.

The composition of residue in reboiler versus time is shown in Fig .6. As the reaction precedes the composition of the methyl acetate and water increased in the reboiler up to 180 min. After 180 min the methyl acetate composition could have decreased due to fast separation into vapor phase at solution temperature going much above its boiling point.

The composition of instantaneous distillate versus time is shown in Fig. 7. It can be observed that the mole fraction of methyl acetate is much higher (0.75) compared to the equilibrium mole fraction (0.345) obtained in a batch reactor. Such experimental dynamic data helps in designing large scale batch reactive distillation process.

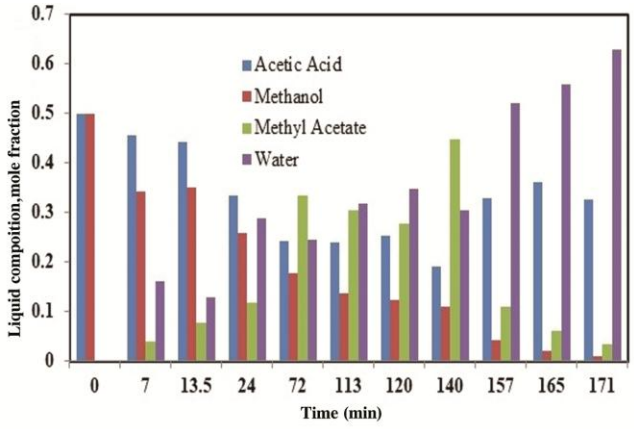

Fig. 6 — Composition of residue for simultaneous reaction and distillation

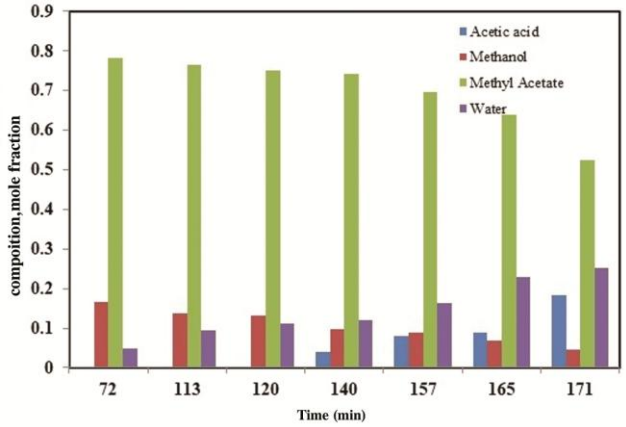

Fig. 7 — Composition of instantaneous distillate for simultaneous reaction and distillation

Conclusion

The production of the methyl acetate in presence of ion exchange resin catalyst Indion 180 in a simple batch distillation apparatus by two methods namely simultaneous and sequential reaction and distillation processes were reported. Mole fraction of methyl acetate in instantaneous distillate is the highest as 0.782 from sequential reactive distillation with 1:1 reactant mole ratio of acetic acid and methanol. Reactive distillation also presents interesting temperature and composition dynamics with regard to distilling the product. Methyl acetate could be produced in high purity by simple distillation conducted after reaction and it is found to be 0.847. From the experimental studies it was found that the purity of methyl acetate in instantaneous distillate of reaction followed by distillation and simultaneous reaction and distillation are comparable but the temperature dynamics of the reboiler has to be followed for an industrial process based on the choice.

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Review Article

A review on the biodiesel production: Selection of catalyst, Pre-treatment, Post treatment methods

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ABSTRACT

As the world grapples with the urgent need for sustainable energy sources, biodiesel production from waste cooking oil (WCO) has emerged as a promising solution. This paper delves into the comprehensive journey of biodiesel synthesis, from feedstock selection and pretreatment to catalysis, post-treatment, and its effects on diesel engines. The role of catalysts, including the exploration of nanoscale catalysts and enzymatic approaches, is scrutinized for efficiency and cost-effectiveness. Biodiesel's character is revealed through rigorous characterization techniques, shedding light on properties crucial for engine performance. Additionally, the paper investigates the production of oxygenated fuel additives from by-products like glycerol and their impact on combustion and emissions. In conclusion, biodiesel, particularly when derived from WCO, emerges as a compelling alternative to conventional diesel, with the potential to reshape the future of sustainable transportation fuels and mitigate environmental challenges.

1. Introduction

Fuel consumption is often used as an indicator of a country's economic progress, given its crucial role in various industries, particularly transportation, where there is a substantial reliance on diesel fuel [1–3]. However, this dependence on diesel has raised significant concerns due to the emission of toxic gases during combustion, contributing to global warming through the greenhouse effect [4,5].

Amidst growing environmental challenges, there has been a surge in research aimed at developing renewable and sustainable alternatives to mitigate the depletion of non-renewable fossil fuels [5]. In response to this need, biodiesel has emerged as a promising biomass-derived biofuel. Biodiesel offers a non-toxic and biodegradable substitute for conventional diesel fuel. The most economically viable method for its production involves transesterification, typically utilizing base catalysts such as NaOH and KOH.

One of the byproducts of biodiesel production is glycerol, accounting for approximately 10% of the biodiesel manufacturing process [6]. This process is characterized by the presence of several contaminants, including free fatty acids, water, methanol, detergent, catalyst residues, and salt [7,8]. The presence of these contaminants complicates the glycerol purification process, adding to its technical intricacy and economic challenges. The increasing demand for biodiesel has led to a proliferation of glycerol production, further jeopardizing the economic viability of the biodiesel industry.

Biodiesel is regarded as a sustainable substitute for conventionally-produced diesel, offering reduced greenhouse gas emissions and environmental friendliness due to its renewable nature [9]. Moreover, biodiesel production has positive environmental and socio-economic impacts, creating employment opportunities across various economic sectors. Biodiesel is essentially composed of alkyl esters derived from triglycerides found in vegetable oils or animal fats [5,10]. The production process involves the transformation of triglycerides into diglycerides, followed by the conversion of diglycerides into monoglycerides, yielding glycerol and biodiesel under optimal reaction conditions, facilitated by an appropriate catalyst.

In the present article, the production of biodiesel is described in presence of various catalysts and no such studies available in the literature. The pre-treatment and post treatment process methods have discussed in detail for obtaining the pure biodiesel. The various methods and role of catalysts and selection of catalysts based on the condition of feed have explained clearly. Production of oxygenated fuel additives have discussed.

2. Production of biodiesel process

Biodiesel presents an excellent alternative to petroleum-based diesel fuel, offering the advantage of seamless integration into compression ignition engines with little to no modification, thereby contributing to improved emissions. The production of biodiesel from various feedstock sources encompasses a range of methods [11,12]. These methods include micro-emulsions, dilution, transesterification employing both catalytic and supercritical approaches, and the incorporation of microwave technology to enhance the process [5,12,13].

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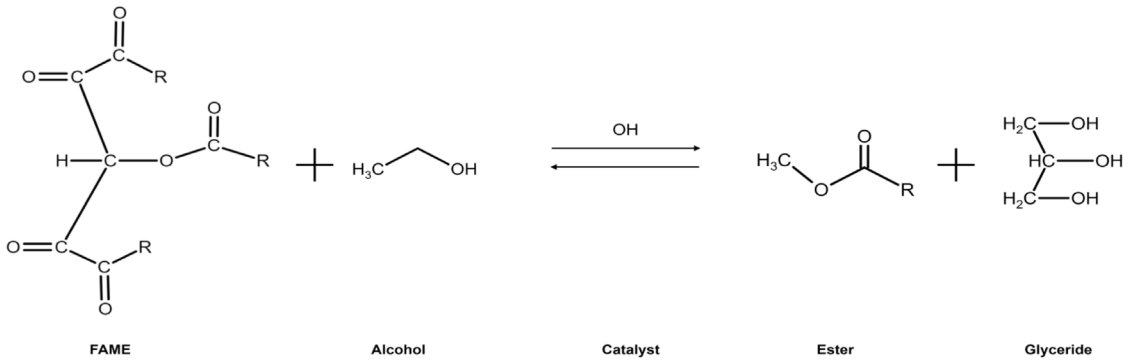

Fig. 1. Trans esterification reaction for biodiesel synthesis [13].

Fig. 1 shows the trans-esterification reaction for the biodiesel production. Transesterification stands out as the most widely employed method in biodiesel synthesis due to its economic viability, particularly when produced at industrial scales [11,14]. This method involves the reaction of oil or fat derived from feedstock with alcohol in the presence of a suitable catalyst. To address the challenge of low miscibility between solid catalysts and the liquid phases of oil and alcohol in standard mixing systems, process intensification techniques such as ultrasonic cavitation and microwave technology are utilized [5].

The utilization of active catalysts, pressure reactors, high temperatures, and rapid stirring rates [5,15] in process intensification often comes at the cost of increased energy consumption, potential impacts on product quality, and higher reactant expenses. In this context, microwave and ultrasonication technologies emerge as valuable tools for process enhancement [5,16].

Microwave technology offers advantages such as rapid reaction times and reduced heat loss. However, it should be noted that the catalyst's activity may continue to influence the conversion process after its withdrawal. Ultrasonication, also known as acoustic cavitation, presents a promising, environmentally friendly, and effective technique for biodiesel production. It capitalizes on the rupture of the immiscible layer between alcohol and oil during cavity collapse, generating highly disruptive forces and ensuring the uniform dispersion of reactants, thereby enhancing reaction yields and kinetics.

When transesterification is employed for biodiesel production, two primary processes are used: catalytic transesterification and supercritical methanol transesterification [5,17].

Supercritical fluids are utilized for biodiesel production in the absence of catalysts. This approach results in rapid reaction rates and high conversion efficiency without the need for a catalyst. However, it does demand a considerable amount of energy and incurs a high installation cost. During supercritical transesterification, a single-phase mixture is formed at approximately 350 °C with a decrease in the alcohol's dielectric constant. The reaction completes in about 3 min [5,18] at the supercritical stage, and product purification is straightforward due to the absence of a catalyst. Nevertheless, manufacturing costs remain relatively high.

Catalytic transesterification involves the exchange of alkyl groups (R) between esters and alcohols, yielding fresh esters (biodiesel) and alcohol (glycerol). This process comprises two fundamental stages:

Formation of an alkoxide ion when alcohol reacts with the catalyst.

Creation of a methoxide ion when methanol is employed as a solvent, followed by the reaction of an alkoxide ion with triglycerides in oil to produce fatty acid alkyl esters. Methanol releases hydrogen ions, while the base (e.g., NaOH or KOH) contributes hydroxides. This results in the fusion of protons [5].

Water is generated by the reaction of hydroxyl (from the alkali) and OH (from alcohol). Metal ions liberated from the base react with free fatty acids to form soap. Excessive water in the reaction mixture is responsible for this undesirable saponification reaction, highlighting the necessity of a water-free medium to prevent saponification.

The biodiesel life cycle as shown in Fig. 2, embodies a captivating synergy between scientific precision and environmental stewardship. Commencing with the cultivation of renewable feedstocks such as soybean oil or waste cooking oil, a cascade of biochemical reactions ensues, culminating in the production of a remarkably sustainable fuel. Through intricate processes like transesterification, raw materials are chemically transformed into biodiesel, while glycerin is co-produced as a valuable byproduct. Rigorous analyses, encompassing life cycle assessments, energy balances, and emission inventories, unveil biodiesel's environmental merits. By reducing net carbon dioxide emissions and mitigating the release of harmful pollutants, this biofuel epitomizes a triumph of ecological engineering, harmonizing human progress with ecological equilibrium, and heralding a promising era of low-carbon transportation.

The flowchart for biodiesel production as shown in Fig. 3, presents a meticulous depiction of the intricate processes involved in transforming renewable feedstocks into a sustainable fuel. Beginning with the collection of feedstocks such as vegetable oils or animal fats, a series of critical steps ensue. The feedstocks undergo pretreatment to remove impurities and contaminants, ensuring optimal conversion. Subsequently, transesterification takes place, where the feedstocks react with an alcohol, typically methanol, in the presence of a catalyst, commonly sodium or potassium hydroxide. This reaction leads to the formation of biodiesel and glycerin as co-products. The mixture is then subjected to separation, with the glycerin extracted for further processing or utilization. Biodiesel undergoes additional refinement processes, including washing to remove any residual impurities and drying to eliminate water content. Finally, the purified biodiesel is ready for distribution and utilization as a clean-burning alternative fuel, significantly reducing greenhouse gas emissions and contributing to a sustainable energy landscape. The flowchart elegantly captures the intricacy and interconnectedness of the various stages involved in the production of biodiesel, exemplifying the convergence of scientific knowledge, chemical engineering, and environmental consciousness.

Different biodiesel process techniques offer distinct advantages and disadvantages, influencing their applicability and feasibility in biodiesel production as shown in Table 1. Transesterification, a well-established technique, boasts high conversion efficiency and compatibility with various feedstocks. However, it requires the use of catalysts, which can be hazardous, and generates waste glycerin, necessitating proper disposal. Supercritical methanol offers faster reaction rates and lower catalyst requirements, reducing soap formation. Yet, it demands specialized infrastructure, poses safety risks due to methanol, and faces scalability challenges. Enzymatic transesterification operates under mild conditions, reduces energy consumption, and yields high-purity glycerin. However, it requires costly enzymes, exhibits slower reaction kinetics, and faces challenges in process scale-up. Considering these trade-offs, selecting the most suitable technique requires careful consideration of feedstock characteristics, process scalability, environmental impact, and economic viability.

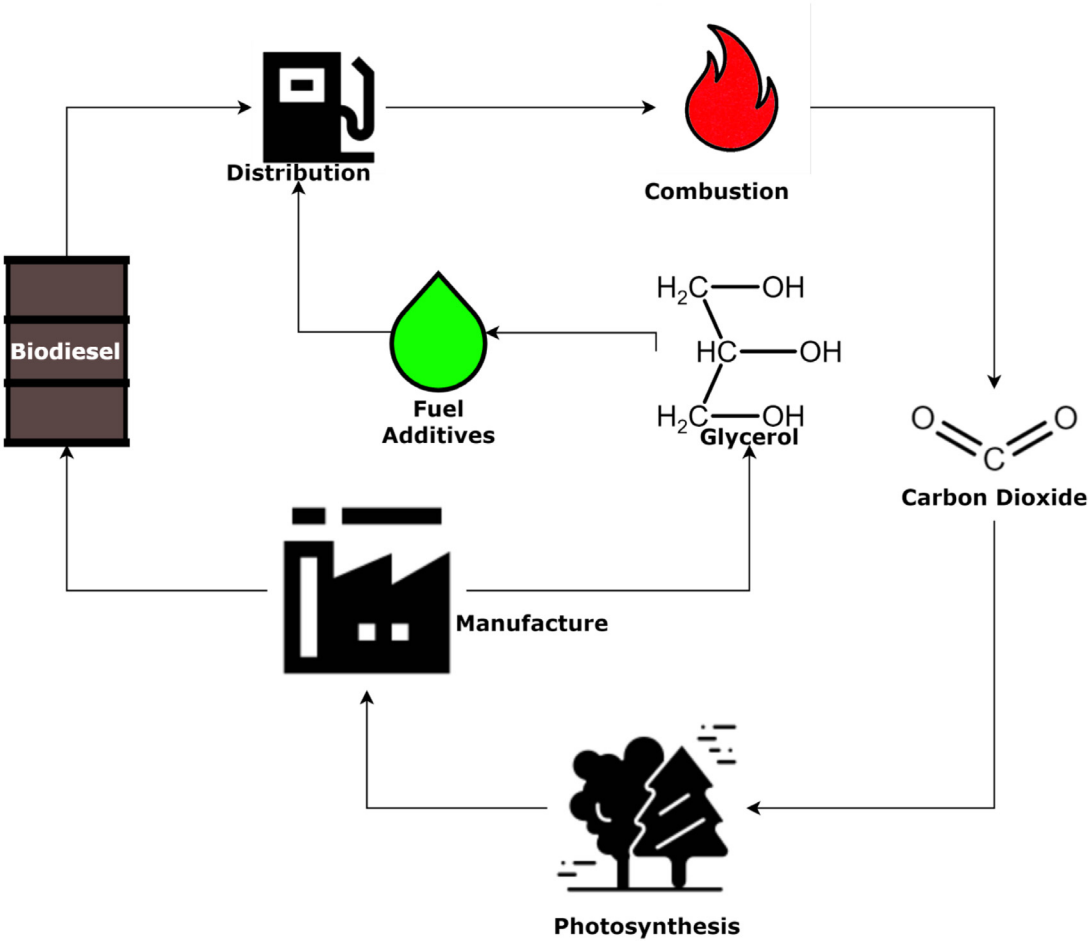

Fig. 2. Biodiesel life cycle.

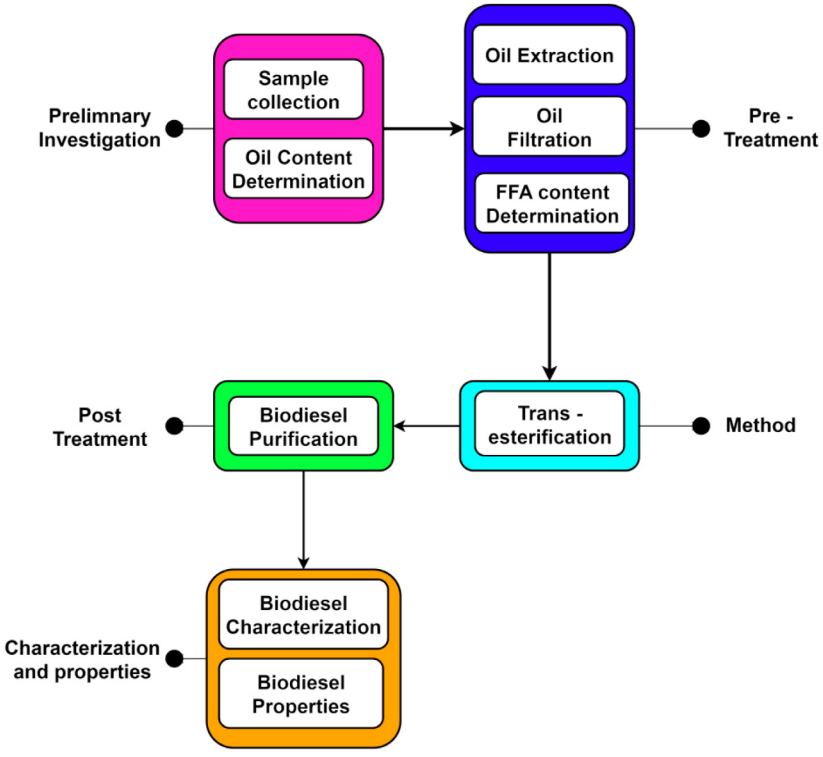

Fig. 3. Flowchart for biodiesel production.

Table 1
Advantages and disadvantages of different biodiesel preparation techniques [19].

Biodiesel techniques	Advantages	Limitations
Trans-esterification	Fuel features that are essentially identical to those of petroleum diesel. Suitable for biodiesel production on a huge scale.	Low oil, water and FFA concentration is necessary. Polluting biodiesel must be washed before use, accompanied by ancillary goods.
On the basis of homogeneous catalysis, trans-esterification	Sufficient response time efficient conversion that is simple to carry out. Inexpensive.	No chance of recovering the catalyst. Saponification. Glycerol of subpar quality is created.
On the basis of heterogeneous catalysis, trans-esterification	High production of biodiesel. Eco-friendly as cleaning is not necessary. Absence of hydrolysis and saponification.	Pricier than homogeneously catalyzed trans-esterification. Increased response time.
On the basis of Enzyme catalyzed, trans-esterification	Oil tolerance for the presence of water. No FFA saponification. Low input/consumption of energy.	High-Priced Enzymes. MeOH-based inhibition Enzymes absorbs glycerol from its surface over a much longer reaction period.
Supercritical/Non catalyzed On the basis of Supercritical/Non catalyzed, trans-esterification	No catalyst is necessary. Simplified product purification. Rapid response time. Water and high FFA have no impact.	Lack of high reaction pressure and temperature. High methanol use. High cost per capita. High energy use.

Table 2
Feed stock selection based on the nature of the catalyst [25–28].

Base catalyst favored	Acid or alcohol catalyst favored
Caprylic acid (C8:0)	Oleic acid (C18:1)
Capric acid (C10:0)	Palmitoleic acid (C16:1)
Myristic acid (C14:0)	Linoleic acid (C18:2)
Palmitic acid (C16:0)	Arachidic acid (C20:0)
Linolenic acid (C18:3)	Stearic acid (C18:0)
Butyric acid (C4:0)	Lauric acid (C12:0)
Behenic acid (C22:0)	EPA (C20:5,n-3)
Stearidonic acid (18:4n-3)	DHA (C22:6,n-3)
Mead acid (20:3n-9)	gamma-linolenic acid (18:3n-6)
Arachidonic acid (20:4n-6)	Dihomo-γ-linolenic acid (20:3n-6)
Docosahexaenoic acid (22:6n-3)	alpha-Linolenic acid (18:3n-3)
Caproleic acid (10:1n-1)	
Lauroleic acid (12:1n-3)	
Myristoleic acid (14:1n-5)	
Elaidic acid	
Gadoleic acid (20:1n-11)	
Erucic acid (22:1n-9)	
Nervonic acid (24:1n-9)	

3. Pre-treatment

3.1. Free fatty acid (FFA) content determination

The nature of feedstock, often sourced from post-consumer outlets, tends to have elevated levels of free fatty acids (FFA) [20–22]. Consequently, the FFA content often exceeds permissible limits for alkaline transesterification, typically defined as having an FFA content of >1%. This excess FFA content results from the concurrent saponification reaction, which occurs directly due to the presence of an alkali or base catalyst [23,24].

To assess FFA content, the acid value test using a titration procedure outlined by ASTM D6751 is commonly employed. A failure to control this undesirable side reaction can lead to the excessive formation of soap, significantly complicating the washing process by causing emulsion formation, ultimately resulting in a substantial reduction in yield. Alternatively, in cases where feedstock exhibits substantial FFA content, acid-catalyzed transesterification presents a viable option. The choice of a suitable catalyst [24] can be guided by the fatty acid profile of the feedstock, with major components often correlating with Table 2.

Table 3 shows the fuel properties of biodiesel produced with different catalysts.

However, it is important to note that acid catalysts and alcohol catalysts generally exhibit lower reaction rates, making alkaline transesterification the preferred choice in most instances. The problematic fatty acids for alkaline transesterification can also be identified using the table. Given these considerations, some level of pretreatment becomes inevitable. Methods available for reducing FFA content in the oil include neutralization and acid esterification [32]. The structure of fatty acids which are present in WCO is shown in Fig. 4.

3.2. neutralization

Saponification reaction is shown in Fig. 5. Neutralization, often referred to as caustic refining, involves the removal of free fatty acids (FFA) through the addition of a base. This step is carried out before the catalyzed trans-esterification reaction, enabling the subsequent removal of formed soap through mechanical separation processes or unit operations. Additionally, neutralization leads to a substantial reduction in the levels of mucilaginous substances, phospholipids, and color pigments [36–40].

3.3. Acid esterification

When the free fatty acid content exceeds 5%, the use of caustic refining becomes impractical due to significant yield losses caused by the emulsification and saponification processes. In such cases, acid esterification offers a viable alternative. Although this method operates at a slower pace, it presents a valuable compromise, yielding a higher overall output. Acid esterification effectively converts free fatty acids into desirable FAMEs (Fatty Acid Methyl Esters) rather than producing a waste product that requires separation [41,42]. Table 4 shows the various feed stocks used by different catalysts. The maximum amount of biodiesel yield is presented in Table 4.

4. Catalyst

4.1. Criterion for selection

A catalyst plays a crucial role in enhancing the rate of a chemical process (r) by reducing the activation energy (A.E) required, all while remaining unconsumed itself. Unlike stoichiometric reactions, where reactants are consumed, a catalyst does not become part of the final products. While the thermodynamics of the reaction may take considerable time to reach equilibrium, the catalyst remains unchanged throughout its operation, a process known as catalysis. Minimal quantities of catalyst are typically required. In the case of transesterification, like many chemical processes, both acidic and basic catalysts facilitate cation reactions. However, acid catalysts tend to slow down reactions and contribute to equipment wear and tear, making them less suitable for large-scale applications. In contrast, basic catalysts are not only cost-effective but also readily available and highly efficient. For base-catalyzed reactions, the requirement for free fatty acids (FFA) is typically limited to 0.5% or less to prevent saponification [43–46].

Optimal biodiesel production can be achieved using low concentrations of sodium alkoxide, resulting in high yields and shorter reaction times. However, the recovery of this compound can be challenging due

Table 3
Fuel properties of biodiesels produced by different catalysts [29–31].

	Hazelnut Oil with NaOH [1]	Rapeseed oil with NaOH [2]	Rapeseed oil with KOH [2]	ESG Oil with Heteropolyacid Solid Catalyst [3]	Soybean Oil with Heteropolyacid Solid Catalyst [3]	Cotton Seed Oil with Heteropolyacid Solid Catalyst [3]
Viscosity at 40 °C	4.128 mm^2/s	4.5 mm^2/s	4.5 mm^2/s	5 mm^2/s	4.08 mm^2/s	4 mm^2/s
Density	873.06 kg/m^3 @ 15 °C	0.86 relative @ 298 K	0.88 relative @ 298 K	0.879 relative @ 15 °C	0.885 relative @ 15 °C	0.874 relative @ 15 °C
Flash Point	177 °C	409 K	410 K	127 °C	69 °C	70 °C
CFPP (cold filter plug point)	−6 °C	–	–			
Average molecular mass	293.800° g/mol	–	–			
Typical formula	C18.76H35.56O2	–	–			
HV (heating value)	39883 kJ/kg	38.8 MJ/L	38.7 MJ/L	38.67 MJ/kg	39.75 MJ/kg	40.32 MJ/kg
Fatty Acid Composition (%)	C16:0 (11.356), C18:1 (74.778), C18:2 (12.203), C18:3 (0.347), C20:0 (0.345), C20:1 (0.509), C22:0 (0.462)	–	–			
Ester Content (%)	–	99.4	99.4			
Pour Point (°C)	–	–	–	−3	−15	−3
Cetane Number	–	–	–	49	48.2	–

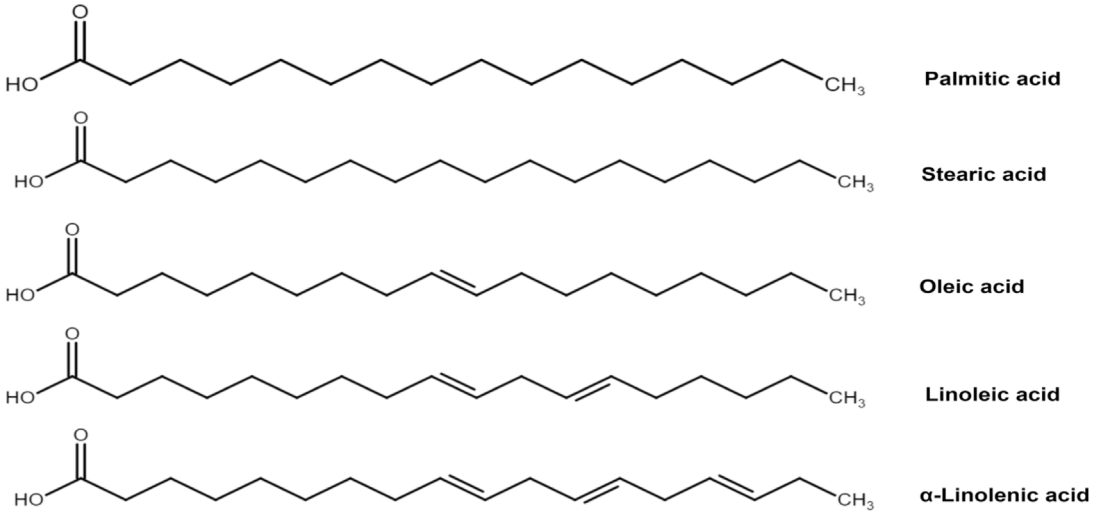

Fig. 4. Common structures of fatty acids present in WCO [33,34].

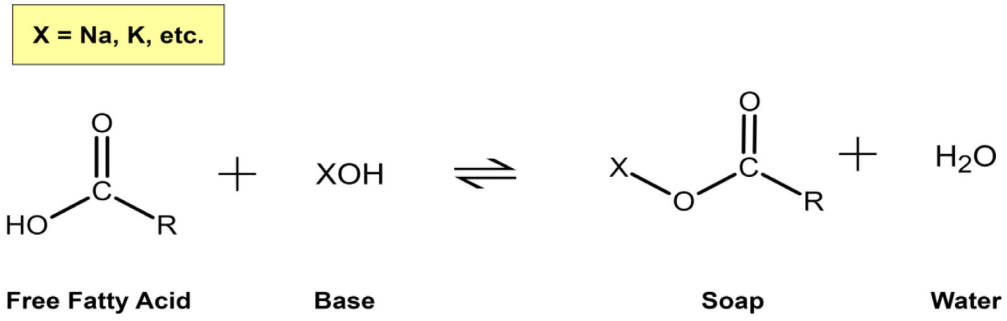

Fig. 5. Saponification reaction [35].

to its tendency to remain unrecoverable. Homogeneous catalysts, on the other hand, offer rapid results with lower concentration requirements but are often challenging to reuse due to recovery difficulties. Therefore, both sodium alkoxide and homogeneous catalysts have their respective strengths and weaknesses, necessitating careful consideration based on the specific requirements of the biodiesel production process [47,48].

In contrast, heterogeneous catalysts are less reactive due to leaching but offer the advantage of being recoverable and reusable. Researchers primarily focus on selecting highly effective and active catalysts to maximize biodiesel production yields. Base catalysts, most commonly sodium and potassium carbonates, generate hydroxides and alkoxides [5], which expedite reactions more efficiently than acid-catalyzed reactions.

Table 4
Examples of different catalyst and feed stock combinations with their yields [5].

Catalyst	Feedstock	Yield
Base Catalyst		
CaO/A1203	Palm oil	98.6
MgZnAIO	Jatropha oil	94
CaO/Kf	Tallow seed oil	>96
CaO	Jatropha oil	93
Mg/Al-hydrotalcite	Soybean oil	90.7
Fe304/CaO	Jatropha oil	95
MgO/Li	Soybean oil	~94
Mg/Al-hydrotalcite	Sunflower oil	75
Al-Ca/K2CO3	Soybean oil	95.1
Na-SiO2	Jatropha oil	98.5
Sodium silicate	Soybean oil	~100
Acid Catalyst		
Zeolite X	Sunflower oil	~95
SO4/ZrO2	Palm oil	90
WO3-ZrO2	Sunflower oil	97
KSF clay amberlyst	Jatropha oil	70
SO4(2-)/TiO2-SiO2	Cottonseed oil	92
SO4(2-)/ZrO2-SiO2	Rocket seed oil	~88
Carbohydrate derived catalyst	WCO	92
Zr0.7H0.2PW12040	WCO	99
ZS/Si	WCO	98

Catalysts with large surface areas have the potential to address various challenges associated with different catalytic types. Nanoscale catalyst synthesis meets these requirements and may be the optimal choice for producing high-quality biodiesel with maximum yield while minimizing costs and time [47,48].

Additionally, enzymes or biocatalysts can produce highly pure and cost-effective products that are easy to separate and operate under mild reaction conditions.

4.2. Advantages and disadvantages of various catalysts

The biodiesel production process involves chemical reactions like esterification and transesterification, both of which employ catalysts, including homogeneous and heterogeneous variants. This encompasses both chemical and biological catalytic systems.

Homogeneous catalysts, while effective, have certain drawbacks, such as the need for water purification and the generation of unreacted compounds. On the other hand, heterogeneous catalysts employ a porous solid support with an external surface, but they are susceptible to leaching, which can adversely affect the reaction. Nanotechnology has emerged as a solution to address challenges associated with both homogeneous and heterogeneous catalysts through the development of nano-catalysts.

In comparison to homogeneous, heterogeneous, and nano-catalysts, solid acid and solid base catalysts based on materials like ash, clay, and organic sources from animals and plants have demonstrated high efficiency [5,47,49].

Biological systems often benefit from free enzymes, which are advantageous due to their functionality, but they tend to be expensive and non-reusable. To circumvent this, immobilized enzymes, which are covalently bonded, are preferred. Immobilization helps avoid leaching issues associated with free enzymes.

To achieve optimal biodiesel production, it is crucial to select the right combination of catalysts, oils, and process conditions. Careful consideration of these factors can lead to the highest possible biodiesel yield.

5. Post treatment

Biodiesel production predominantly revolves around the transesterification reaction, a process that entails the interaction of triglycerides with alcohol in the presence of a catalyst. In the aftermath of this reaction, the presence of residual sodium salts and soap formation poses a concern [50], primarily due to their solubility in water.

To address this issue, an alternative technique known as dry washing has been introduced, replacing traditional water washing methods [51,52]. Dry washing methods employ substances such as magnesol powder, ion exchange resins, and acid clay, among others. These materials serve to eliminate residual sodium salts and soaps, ensuring the quality and purity of the biodiesel product.

5.1. Biodiesel dry washing process

The refinement of biodiesel is shown in Fig. 6. Dry washing stands out as an effective and efficient method for reducing glycerides and total glycerol in biodiesel, simultaneously enhancing fuel quality while minimizing waste-water generation. Unlike traditional methods, dry washing is waterless and offers space-saving advantages by minimizing the surface area coverage of the wash tank. This process ensures low water content, meeting the stringent standards specified by ASTM D6751 [50,53,54]. In fact, studies have shown that Magnesol exhibits properties closely aligned with the ASTM D6751 values.

In a typical batch reactor setup, crude biodiesel is subjected to dry washing with varying concentrations. Samples are periodically withdrawn from the reactor at different time intervals during the washing process [55].

Through extensive experimentation, it has been determined that Magnesol, when used at specific concentrations and speeds, provides optimal results in meeting international standards, such as EN 14214, for refining biodiesel. Additionally, various adsorbents, including activated carbon, activated clay, activated fibers, and acid clay, have been employed for biodiesel refinement. Glycerol, acting as a solvent, is utilized to remove contaminants from biodiesel [47]. In cases where biodiesel is derived from sources with high acidity, alternative methods like diatomaceous earth, impregnated activated carbon, and bleaching with activated carbon have been employed for refinement [50,56].

Furthermore, experiments have been conducted utilizing silica gel as an adsorbent for refining biodiesel. The adsorption process has demonstrated remarkable efficacy in significantly reducing glycerides and removing almost all glycerol from the biodiesel [55,57].

5.2. Membrane separation process

Membrane filtration processes come in various module configurations, including flat plate, hollow fiber, spiral wound, and revolving devices. Tubular modules are particularly favored when a turbulent flow regime is required [58]. These tubular modules typically consist of a semipermeable membrane cast inside a porous support tube, often constructed from stainless steel and enclosed within a perforated pipe. Stainless steel permeate shrouds hold the tubes together, and they vary in diameter and length [58,59].

One notable advantage of tubular modules is their ease of cleaning, and they benefit from a wealth of operational knowledge. However, their primary drawback is the relatively limited membrane surface area [56]. Membrane filtration operates by selectively preventing undesirable materials from passing through a semipermeable barrier, allowing for the separation of solution components. Various factors, including the diffusion of specific molecules, temperature or pressure gradients, and concentration differences, can influence membrane-based transport [55].

Although membrane technology has found extensive application in water purification, gas separation, and protein separation, its commercial use has been primarily limited to aqueous solutions and relatively inert gases. Consequently, employing membrane technology for the treatment of non-aqueous fluids represents a relatively recent area of research [55].

In pressure-driven separation processes, membranes such as reverse osmosis (RO), ultrafiltration (UF), and microfiltration (MF) play pivotal

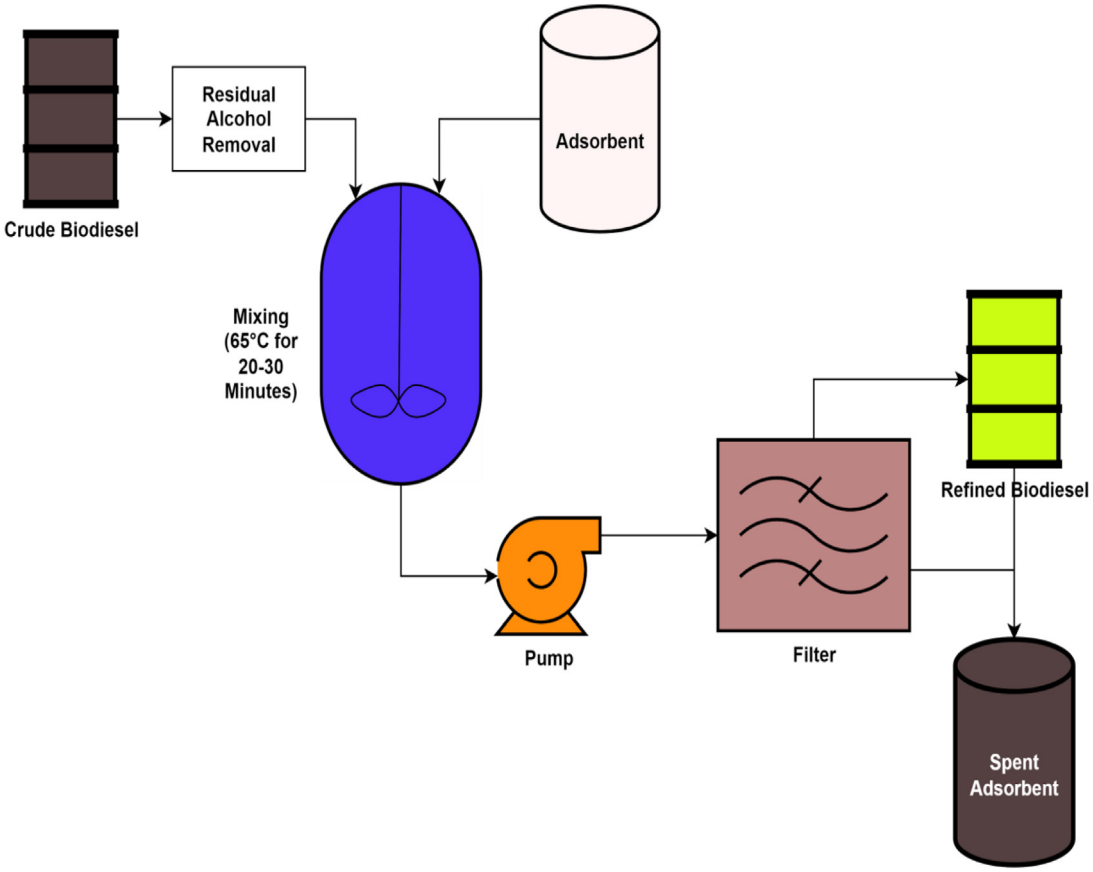

Fig. 6. Refinement of biodiesel.

roles [52,55,56]. These membrane-based separation methods primarily rely on size exclusion, with components separated based on their forms, sizes, or weights. Factors influencing membrane performance include interactions between the membrane surface and feed components, flow velocity, temperature, pressure, and membrane composition [55].

Fig. 7 shows the membrane separation process. Membranes can be categorized into two types: organic and inorganic. Ceramic membranes, such as those composed of Al2O3, TiO2, ZrO2, and SiC, have garnered significant attention due to their superior performance compared to organic membranes. They exhibit enhanced fouling resistance, extended lifespan, and a narrower distribution of mechanical, thermal, and chemical pore sizes. Ceramic membranes also possess microbial degradation resistance, high flux, and high porosity [55,56]. Among organic membranes, polysulfide, polyamide, polycarbonate, and various advanced polymers are commonly employed. Many of these synthetic polymers offer increased microbial degradation resistance and chemical stability [55].

For instance, polyacrylonitrile (PAN) membranes are known for their porous and asymmetric nature, combining good selectivity and penetration rate. However, polymeric membranes may experience expansion, resulting in immediate or persistent pore-size alterations, leading to a relatively short lifespan in solvent applications.

The authors [60] investigated the removal of soap from crude oil using a DES-based ELM/AC, which was a deep eutectic solvent (DES) -based emulsion liquid membrane with the presence of activated carbon (AC). The author observed that removal efficiency of soap of 99.75% obtained by using DES based membrane technique.

The conventional biodiesel production with homogeneous based catalyzed transesterification is replaced by membrane reactor in which heterogeneous catalyst was immobilized [61]. The conversion of 94% achieved by using this mechanism with MnO2 as a nano catalyst.

Esterification with phosphotungstic acid/poly (ether sulfone) (PWA/PES) membrane, transesterification with alkalized polysulfone (APSF) membrane and Graphene Oxide/poly (vinylidene fluoride) (GO/PVDF) separation membrane process integration was studied to produce biodiesel from acidic oil [62]. The authors found that conversion obtained by esterification and transesterification was 98.6% and 91.2% respectively.

The authors [63] presented a review article on membrane technology for the biodiesel separation from the production mixture which contains impurities. The suggested that membrane technology is advantages over conventional process. It is a eco sustainable and the water consumption (0.05–0.1 g water/1 g biodiesel) is hundred times lower than conventional processes.

5.3. Production of oxygenated fuel additives

5.3.1. Residual glycerine

During the production of biodiesel through transesterification, crude glycerine is generated as a by-product. However, this glycerine is in its crude form and requires processing before it can be converted into oxygenated fuel additives that enhance the properties of the resulting diesel fuel [64].

5.3.2. Purification of residual glycerine

The purification of crude glycerol involves a combination of physical, chemical, and solvent extraction processes. This purification process necessitates the use of a polar solvent and an acid in conjunction with the glycerine. Subsequently, the separated salt is typically isolated through techniques such as centrifugation and extraction [65–68].

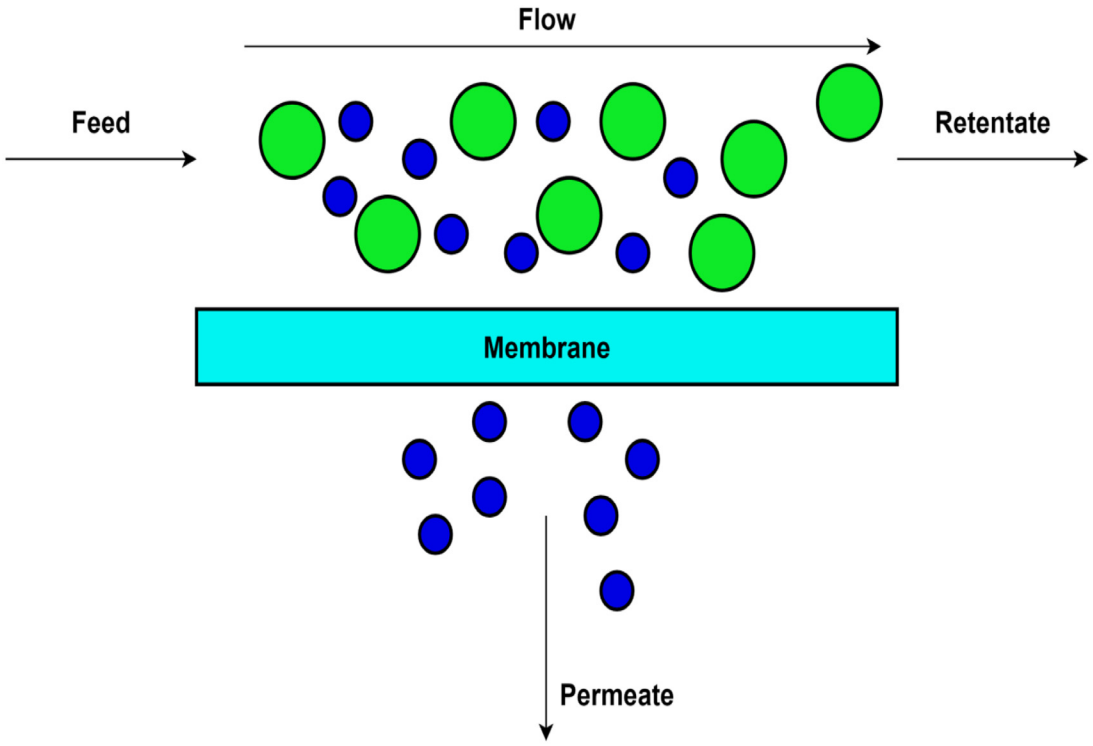

Fig. 7. Membrane separation.

5.3.3. Production of additives

The esterification of glycerol was explored through a series of experiments conducted in a batch reactor equipped with a temperature controller and a water-cooled condenser. The experimental parameters investigated included reaction time and temperature, with the molar ratio of AA/glycerol or AH/glycerol and catalyst loading determined based on previous studies. The experiments utilized USP glycerine, and Amberlyst-15 served as the catalyst. Once optimal conditions were established, both purified glycerine and commercial USP glycerine were subjected to esterification using both biocatalysts and Amberlyst-15. It is worth noting that all experiments were conducted in pairs to ensure the accuracy and reliability of the results [69–72].

5.4. Use of glycerol derivatives in diesel engines

The influence of glycerol-based oxygenated additives on combustion pressure in diesel engines has been a subject of on-going debate among researchers. While some studies have reported a decrease in combustion pressure when glycerol derivatives are introduced into diesel–biodiesel blends, others have observed the opposite effect. The distinct properties of glycerols, including high volatility, lower viscosity, and a high oxygen content, have the potential to enhance the premixed combustion phase, possibly leading to higher combustion pressure [73–75]. Conversely, certain glycerol derivatives have been found to reduce the heat release rate when added to diesel–biodiesel blends. This can be attributed to their higher latent heat of vaporization, which slows down the combustion process and diminishes the heat release rate. In summary, these additives have demonstrated the ability to shorten the combustion duration of diesel–biodiesel blends by approximately 5%, showcasing their potential as effective combustion modifiers [8,76].

The combustion process within fuel blends involves the conversion of carbon content into CO2, the concentration of which in exhaust gas depends on various factors, including carbon atoms, C/H ratio, density, and oxygen content. Intriguingly, research has indicated that the inclusion of specific glycerol derivatives in diesel–biodiesel blends may actually reduce CO2 emissions. This effect can be attributed to the higher latent heat of vaporization of certain glycerol derivatives, which can lower in-cylinder temperatures and lead to incomplete combustion. Furthermore, aromatic-free glycerol derivatives' oxygen content can aid in reducing the formation of unburnt hydrocarbons (UHC) in diesel–biodiesel blends. Additionally, glycerol derivatives can expedite the combustion process in rich air-fuel mixture regions by accelerating oxidation. However, it is important to note that increasing the oxygen content of fuel blends may reduce their heating value, consequently lowering combustion temperature and increasing UHC emissions [8,77–80].

5.4.1. PM emissions

Incorporating glycerol derivatives into diesel–biodiesel blends has proven to be an effective strategy for reducing particulate matter (PM) emissions. This reduction is likely attributable to the high oxygen content of glycerol ethers, which promote complete combustion and mitigate PM formation. Additionally, the reduced number of carbon molecules and polycyclic aromatic hydrocarbons found in glycerol derivatives can also contribute to the decrease in PM emissions. Overall, these findings suggest that the utilization of glycerol derivatives in diesel–biodiesel blends can have a significantly positive impact on air quality by reducing PM emissions [8,77].

5.4.2. NOx emission

The effects of glycerol-based oxygenated additives on nitrogen oxide (NOx) emissions in diesel engines have generated varying results and remain a subject of debate. Some studies have reported a decrease in NOx emissions when such additives are introduced into diesel–biodiesel blends, while others have observed the opposite effect. These varying effects can be attributed to several factors, including the oxygen content of specific compounds. Compounds with a high oxygen content can elevate the maximum local temperature during combustion, potentially stimulating NOx formation. Furthermore, some of these compounds have been found to increase peak in-cylinder pressure, accelerate the heat release rate, shorten combustion duration, and enhance atomization/mixing—all of which can promote NOx formation.

Table 5
Identification of different functional groups based on the wavelength number [88–90].

Wavenumber (1\cm)	Functional group
3000–2850	alkanes - stretch
1450–1375	alkanes - bend
3100–3000	alkenes - stretch
1000–650	alkenes - bend
3150–3050	aromatic - stretch
900–690	aromatic - bend
3300	alkyne - stretch
2900–2800	aldehyde
1680–1600	alkene
1600–1475	aromatic
2250–2100	alkyne
1740–1720	aldehyde
1725–1705	ketone
1725–1700	carboxylic acid
1750–1730	ester
1680–1630	amide
1810–760	anhydride
1800	acid chloride
1300–1000	all C–O groups
3650–3600	alcohols, phenols
3400–3200	H-bonded alcohols, phenols
3400–2400	carboxylic acid
3500–3100	all nitrogen groups - stretch
1640–1550	all nitrogen groups - bend
1350–1000	amines

Clearly, additional research is needed to comprehensively understand the impact of glycerol-based oxygenated additives on NOx emissions in diesel engines [8,77].

5.5. Effects of derivatives on the performance of diesel engines

The impact of glycerol-based oxygenated additives on the Brake Thermal Efficiency (BTE) of diesel engines remains a topic of discussion, with no clear consensus in the research findings. Some studies have suggested that the addition of specific glycerol derivatives to diesel–biodiesel blends can enhance fuel conversion efficiency and increase the engine's BTE. This improvement could be attributed to factors such as higher structural oxygen content, reduced viscosity, and an elevated Cetane index (8). Glycerol-derived additives have demonstrated the potential to elevate the performance, combustion characteristics, and exhaust emissions parameters of diesel engines by more than 3.5% [8,81–83].

Conversely, other investigations have indicated that the inclusion of certain glycerol derivatives in diesel–biodiesel blends may result in a reduction in Brake Specific Energy Consumption (BSEC) for diesel engines. The oxygen-rich nature of particular glycerol derivatives might be a contributing factor to this outcome. In general, these additives have the capacity to lower in-cylinder temperatures and reduce the rate of power generation [8,84–87].

These findings illustrate that the effects of glycerol-based oxygenated additives on diesel engine performance are multifaceted and can vary based on several factors. Further research is essential to gain a comprehensive understanding of the precise impact of these additives on engine efficiency and emissions.

6. Biodiesel characterization

6.1. FT-IR spectroscopic study

FT-IR spectroscopy, or Fourier-transform infrared spectroscopy, is a powerful analytical tool used for characterizing compounds based on their absorbance spectra and FTIR. Compared to traditional spectrophotometers, FTIR provides rapid acquisition of infrared (IR) spectra. This technique employs a high-intensity black-body source to emit an IR radiation beam, which is subsequently modulated by an interferometer [88]. As the beam passes through a sample, specific frequencies of energy are absorbed, a unique characteristic of the sample, and a detector monitors the intensity versus time for all frequencies. A reference beam is also incorporated for instrument calibration [88–92].

Following automatic background subtraction by the interferogram, the desired spectrum is obtained through Fourier transformation using computer software. FTIR spectroscopy is capable of offering comprehensive qualitative and quantitative information on various chemical systems. It is often used in the analysis of byproducts from biomass thermochemical processes, providing precise insights into surface and bulk chemical structures. In the examination of FTIR spectra, peak ratios or identifiable individual peaks are selected for analysis, but it necessitates a fundamental understanding of significant spectral properties. Concentrations of thermal breakdown products can be estimated by comparing FTIR data with calibration spectra obtained under identical conditions, and a list of common bond types with their respective wavenumbers is provided [88,89].

Table 5 shows different functional groups identification based on the wavelength numbers.

Table 6
ASTM standards and testing methodology for different Biodiesel properties [97–100].

Properties (Units)	Test method	
	ASTM	EN
Viscosity kinematic at 40 °C (mm^2/s)	D 445	EN ISO 3104
Density at 15 °C (kg/m^3)	D1298	EN ISO 3675/12185
Calorific value (MJ/kg)	–	EN 14214
Flash point (°C)	D 93	ISO DIS 3679
Pour point (°C)	D 97	–
Cloud point (°C)	D 2500	–
Oxidation stability hours, 110 °C	D 675	EN 14112
Cetane number	D 613	EN ISO 5165
Acid value (mgKOH/g)	D 664	EN 14104
Water content (%V)	D 2709	EN ISO 12937
Canradsons carbon residue (m/m)	D 4530	EN ISO10370
Sulphated ash (% m/m)	D 874	EN ISO 3987

6.2. NMR (Nuclear Magnetic Resonance) spectroscopic analysis

Nuclear Magnetic Resonance (NMR) spectroscopy including proton (1H), carbon-13 (13C), and phosphorus-31 (31P) NMR, presents a promising avenue for the determination of free fatty acids (FFA) in oils and fats. NMR spectroscopy offers several advantages for this purpose, making it an attractive analytical technique. These advantages include its non-destructive and non-invasive nature, speed and simplicity, and its capacity to provide comprehensive compositional information about a mixture in a single spectrum without necessitating sample derivatization or extensive pre-treatment. Additionally, NMR analysis typically requires minimal sample preparation and only small quantities of organic solvents or reagents. NMR is inherently quantitative, as the integral of a signal directly correlates with the number of corresponding nuclei, assuming the experimental parameters meet specific criteria [31,93–96].

As a result, NMR spectra allow for the direct extraction of molar concentrations. This technique is especially valuable for analyzing substances that cannot be studied using chromatographic methods due to factors like heat sensitivity or other limitations. Over the years, NMR spectroscopy has established itself as a powerful method for characterizing fatty acids and determining their composition [31,96].

6.3. Analysis of biodiesel properties

The biodiesel properties tested as per the ASTM standards as shown in Table 6.

Table 7
An overview of commonly used prediction methods for key biodiesel fuel properties [100–104].

Source	Fuel properties predicted	Data used
[100]	Density and Refractive Index	Horizontal Attenuated Total Reflectance Mid-Fourier Transform Infrared (HATR/mid-FT-IR) Spectroscopy Data
[100]	Cold Filter Plugging Point (CFPP)	Horizontal Attenuated Total Reflectance Mid-Fourier Transform Infrared (HATR/mid-FT-IR) Spectroscopy Data
[101]	Cetane Number (CN), Various metrics or properties of biodiesel	Fatty Acid (FA) Composition
[101]	Cetane Number (CN), Various metrics or properties of biodiesel	Fatty Acid (FA) Composition
[101]	Cetane Number (CN), Various metrics or properties of biodiesel	Fatty Acid (FA) Composition
[101]	Cetane Number (CN), Various metrics or properties of biodiesel	Fatty Acid (FA) Composition
[102]	Cetane Number (CN), Flash Point (FP), Kinematic Viscosity (KV), Density	Fatty Acid (FA) Composition
[103]	Higher Heating Value, Oxidation Stability, Kinematic Viscosity	Characteristics of Various Fatty Acid Alkyl Esters (Basic Molecular Structures of Biodiesel), Composition of Fatty Acid Alkyl Esters Analyzed for Prediction, Experimental Data for Fuel Properties (Comparison and Validation)
[104]	Density, Kinematic Viscosity, Viscosity–Density Correlation	Volume Fractions of Biodiesel, Temperature, Experimental Data with High R^2 Values for Each Property Prediction

6.3.1. Kinematic viscosity

Kinematic viscosity is a measure of a fluid's internal resistance to flow under the influence of gravity. It is determined by measuring the time it takes for a specific volume of fluid to pass through a standardized aperture. High viscosity in biodiesel can lead to problems such as improper atomization, engine deposits, and soot buildup. Lower kinematic viscosities are generally preferred as they allow for easier pumping and produce the desired droplet sizes at the injector. Two commonly accepted methods for measuring the kinematic viscosity of biodiesel are ASTM D445 and EN ISO 3104. Biodiesel's viscosity is reported to be similar to that of mineral diesel in some studies. The alkali-catalyzed transesterification process significantly reduces the viscosity of biodiesel. It should be noted that biodiesel's viscosity tends to increase with a higher content of double bonds. Elevated viscosity levels can impact engine volumetric flow and injection spray properties, and at low temperatures, it may even pose risks to the mechanical integrity of the injection pump's drive systems [105].

6.3.2. Density

Density is a crucial physical parameter for determining the volume of fuel required for proper combustion. It plays a role in fuel atomization and can affect the performance of airless combustion systems. Biodiesel fuels typically exhibit higher densities than conventional diesel fuel, which can influence their effectiveness in the engine. The density of biodiesel can be measured using ASTM D1298 and EN ISO 3675/12185 test procedures and should meet established standards. Biodiesel density typically falls within the range of 869.0–877.4 kg/m^3, with densities potentially increasing in the presence of unsaturated acids containing more than two double bonds. Elevated biodiesel densities can lead to challenges such as poor vaporization and incomplete combustion of the injected fuel [98].

6.3.3. Flash point

The flash point of biodiesel is an important parameter, as it indicates the temperature at which the fuel can ignite when exposed to an open flame. It is worth noting that the presence of impurities or contaminants, like water, can lower the flash point, making biodiesel more flammable. Standard methods such as ASTM D93 and EN ISO 2719 are employed to measure the flash point of biodiesel. Ensuring that the flash point of biodiesel meets regulatory requirements is essential for safe handling and storage [98].

6.3.4. Cloud point and pour point

The cloud point and pour point of biodiesel are critical for applications requiring low-temperature performance. The cloud point is the temperature at which a cloud of wax crystals first appears as the fuel cools, while the pour point represents the lowest temperature at which the fuel can still flow. The presence of saturated fatty acids in biodiesel tends to raise its pour point. It is worth noting that the cloud point and pour point of biodiesel are often higher than those of conventional diesel fuel. These properties can vary significantly based on the fatty acid compositions of the feedstock used for biodiesel production [98].

6.4. Prediction methods used for the fuel properties of biodiesel

The fuel properties of biodiesel play a crucial role in its performance and compatibility with existing diesel engines and infrastructure. To assess these properties, various prediction methods have been developed to provide valuable insights into the biodiesel's quality and behavior. Table 7 shows an overview of commonly used prediction methods for key biodiesel fuel properties.

7. Conclusion and future challenges

Biodiesel has emerged as a promising and sustainable alternative to conventional diesel fuel when derived from waste cooking oil (WCO). Nonetheless, its effective utilization demands meticulous pretreatment, involving the removal of solid impurities, the reduction of free fatty acid (FFA) content, and the elimination of water content. Techniques like neutralization and acid esterification play pivotal roles in rendering WCO suitable for the transesterification process. By optimizing parameters such as temperature, reaction time, catalyst concentration, and oil-to-alcohol molar ratio, one can yield high-quality biodiesel from WCO. The choice of catalyst assumes paramount importance in biodiesel production. While both acidic and basic catalysts fulfill indispensable roles, basic catalysts, especially sodium and potassium carbonates, are favored for their efficiency and cost-effectiveness. Researchers are actively exploring nanoscale catalysts and enzymatic approaches to further augment biodiesel synthesis. Post-treatment methods like dry washing, membrane separation, and glycerol purification refine biodiesel and expunge impurities, ensuring compliance with regulatory standards and engine performance criteria. Several pressing challenges remain on the scientific and industrial fronts, such as feedstock sustainability, economic viability and waste management.

Abbreviations

Abbreviation	Definition
WCO	Waste Cooking Oil
FFA	Free Fatty Acids
AE	Activation Energy
r	Rate of chemical process
BTE	Brake Thermal Efficiency
C/H	Carbon/Hydrogen
UHC	Unburnt Hydrocarbons
PM	Particulate Matter
NO_X	Nitrogen Oxides
BSEC	Brake Specific Energy consumption
FT-IR	Fourier-transform infrared spectroscopy
NMR	Nuclear Magnetic Resonance
EN	European Norm
ASTM	American Society for Testing and Materials
ISO	International Organization for Standardization
CO	Carbon Monoxide
CO_2	Carbon Dioxide
H_2O	Water
CH_4	Methane
C_2H_4	Ethene
SO_2	Sulfur Dioxide
HCN	Hydrogen cyanide
NH_3	Ammonia
NaOH	Sodium Hydroxide
KOH	Potassium Hydroxide
CFPP	Cold Filter Plug Point
HV	Heating Value
PLS	Partial Least Squares
SVM	Support Vector Machine
MLR	Multiple Linear Regression
ANN	Artificial Neural Networks
MAE	Mean Absolute Error

CRediT authorship contribution statement

Sai Mani Yogesh Kosuru: Conceptualization, Data curation, Formal analysis, Methodology. **Yashraj Delhiwala:** Conceptualization, Validation, Writing – original draft, Writing – review & editing. **Prasad Babu Koorla:** Conceptualization, Data curation, Writing – review & editing. **Mallaiah Mekala:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Experimental studies of a continuous catalytic distillation column from startup to steady state for the production of methyl acetate

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Abstract: Esterification of acetic acid with methanol to produce methyl acetate and water has been studied in a continuous packed bed catalytic reactive distillation. The key challenge is the startup method of the experiments fora continuous reactive distillation as well as reactive zone height selection. In the present study, the effect of various operating conditions on the methyl acetate composition (mole fraction) is studied. Indion 180 ion-exchange resin solid catalyst is used in the reactive zone. The catalyst is immobilized by using a novel equivalent Katapak-S in the reactive section. Experiments were performed under different operating conditions to find the high purity methyl acetate product in the distillation. The experiments were performed for various conditions like total feed flow rate, reboiler temperature, reflux ratio, methanol to acetic acid mole ratio and catalyst loading with the time. The experiments were carried out till the system reaches to the steady state under different conditions. The maximum methyl acetate concentration is obtained at 80 °C reboiler temperature, 2.01 reflux ratio, 16.3 g/min flow rate, 60 g catalyst loading and 1 mol ratio of methanol to acetic acid. The highest purity of methyl acetate obtained under optimal condition is 95 % by mole.

Keywords: esterification; resin catalyst; reactive distillation; mole ratio

1 Introduction

In any chemical process, main steps are reaction followed by separation with purification. Distillation is one of the separation processes where high purity of components can be achieved. Distillation of mixture into desired chemicals or components is an energy consumption process. Reactive distillation is a process in which reaction and separation occurs simultaneously in one unit. In reactive distillation, reaction and distillation operations are carried out concurrently; the overall energy demand can be reduced. In the reactive distillation, the reactive zone allows for the reaction of reactants into the products. The products then separated based on their boiling points. The low volatile components are separated in the stripping zone and high volatile components separated in the rectifying zone. The reduction in process units as well as the direct heat utilization for further process in reactive distillation can minimize capital investment along with production costs. When reactions are equilibrium constrained, reactive distillation constantly removes the products from the reaction zone, increase the conversion drastically. Because of continuous separation of products from the reactive zone, the selectivity of the reactions improves drastically. Reactive Distillation (RD) is a viable alternative to traditional processes [1–6] due to the advantages like, reduction in capital cost, decreased energy utilization, improving of yields and purity.

Corrigan and Ferris [7] presented a pilot plant process development of esterification of acetic acid and methanol. The authors investigated and design a reactive distillation process to small scale process at low temperature and low pressure to the esterification reactions. The production of high purity methyl acetate in a reactive distillation column using sulphuric acid catalyst has been investigated by Agreda et al. [8]. The authors performed experiments for the esterification reaction of acetic acid with methanol in presence of homogeneous catalyst at a stoichiometric ratio of reactants. The methyl acetate is collected as distillate and water as bottom product. The authors further studied the process to removal of the intermediate components as a side streams to achieve high purity methyl acetate. A review on the investigation of the methyl acetate synthesis in a heterogeneous catalytic reactive distillation process was published by Bessling et al. [9]. Packed bed reactive distillation column was used for the comparison of experimental data with simulation results to the methyl acetate synthesis at different reflux ratios, mole ratio and packing types.

Popken et al. [10] have performed the experiments for the synthesis as well as hydrolysis of methyl acetate using

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a structured catalytic packing Katapak-S in a packed bed reactive distillation. The removal of dilute acetic acid from water was studied using the catalytic distillation apparatus by Xu et al. [11]. Ion exchange resin catalyst such as Amberlyst 15 was used for removal of acetic acid by allowing reaction between acetic acid and methanol to form methyl acetate in a tray column. They observed that main effective parameters are reflux ratio, acid feed location to column and top product flow rate. Gorak and Hoffmann [12] have studied the catalytic distillation using a structured packing's for the synthesis of methyl acetate. Sandesh et al. [13] have investigated the synthesis of methyl acetate from the liquid phase esterification reaction between acetic acid and methanol by using the ion-exchange resin catalyst in the packed bed reactive distillation column. Indion 190 was used as the ion exchange resin catalyst.

The various types of packing's are available in the literature but structure packing is the one of the advanced packing material used in the packed bed reactive distillation column to keep the catalyst inside the envelopes [14–17].

Previous investigations are related to the carrying of experiments under various conditions to find out the distillate and bottom compositions at steady state. In the present study, all the experiments were conducted to find the purity of methyl acetate in the distillate product with respect to time. For the first time, the detailed experiments under the various conditions are carried out and their influence on methyl acetate composition in the distillate is presented with respect to time in presence of the novel catalyst and structured packing.

The present study focused on production of methyl acetate in the reactive distillation under different operating conditions with Indion 180 novel resin catalyst. In our previous paper both acetic acid conversion and mole fraction of methyl acetate in the distillate has presented at steady state condition. The aim of the present work, to give more experimentation details from the start up condition to the steady state conditions under different parameters. This is novelty of the work where till now no such studies have published.

2 Experimental

2.1 Chemicals & catalysts

The raw materials methanol and acetic acid used for the present investigation have purchased from SDFC Limited, Mumbai, India. These are used as such supplied by supplier. The catalyst, Indion 180 also procured from the same company. Indion 180 has cross links 3D polymeric structures formed by sulfonation of polystyrene/divinyl benzene copolymer. It is a solid spherical bead that is opaque grey color. The physical properties of the solid resin catalyst are described in the previous work [18, 19].

2.2 Experimental setup

Figure 1 shows the laboratory experimental set up of reactive distillation column. The distillation column made up with borosilicate glass of 3 m height and diameter of 5 cm. The reboiler with a 3 L capacity is surrounded by an electrical heat source of 2 kW. Temperature controller of TC544 is used to control the reboiler temperature. The RD column has three zones. Rectifying zone is at the top of the column; reactive zone is in the middle of the column and stripping zone in the bottom of the column. Hyflux packing is used as nonreactive packing in rectifying and stripping zones. Katapak-S structured packing is used in reactive zone in which Indion 180 resin catalyst are filled in this packing. All of the packing materials have supplied by Abhishek Scientific Company, Mumbai. The reactive zone is 1 m height, the rectifying zone is 1 m height and stripping zone is 1 m height. Pt-100 temperature sensors are located in the various locations of the column to measure the temperatures. Asbestos rope is wounded around the column to minimize the heat losses.

2.3 Startup procedure

The reboiler was initially filled with methanol with a capacity of 2.7 L and allowed 30 % of free space in the reboiler. The temperature controller of the reboiler was set to a process value as desired before beginning of experiment. The heater has been turned on and heat is supplied to the reboiler. After 15–20 min, methanol vapors starts moving from the reboiler to column and finally reach to condenser. The column was operated under total reflux condition until a pseudo steady sate temperature reached throughout the column. When the temperatures along column are maintained constant throughout column, it is considered as pseudo steady state.

After 60 min, peristaltic pumps were started to supply both methanol and acetic acid at a pre-calculated flow rates. After 1 h of feed supply, the distillate and bottoms flow rates were adjusted and collected in the receivers. The mass balance was checked to confirm that inlet and outlets of mass should be constant. The samples have collected for every 2 h and tested by Gas Chromatography immediately. The RDC was operated till the steady state. After confirming the steady state, the column was operated for 2 h more to observe the steady state condition. At steady state, the composition, temperature, and total mass flow rates are remain constant with time which confirms that the system reached steady state.

2.4 Analysis

The collected samples have analyzed with a gas chromatography (GC-2014 ATF, Schimadju, Japan). Porapak-Q packed column which is having of 2 m length and 3.17 mm id was used to analyze the sample. The thermal conductivity detector is used. 99.99 % hydrogen used as a carrier gas and maintained at 30.0 ml/min flow rate into the column. The oven temperature was maintained at 323.15 K for 1 min. After that the oven temperature was increased from 323.15–443.15 K at a ramp rate of 10 K/min. Then the column was held at 443.15 K for 2 min. The detector temperature was maintained at 473.15 K.

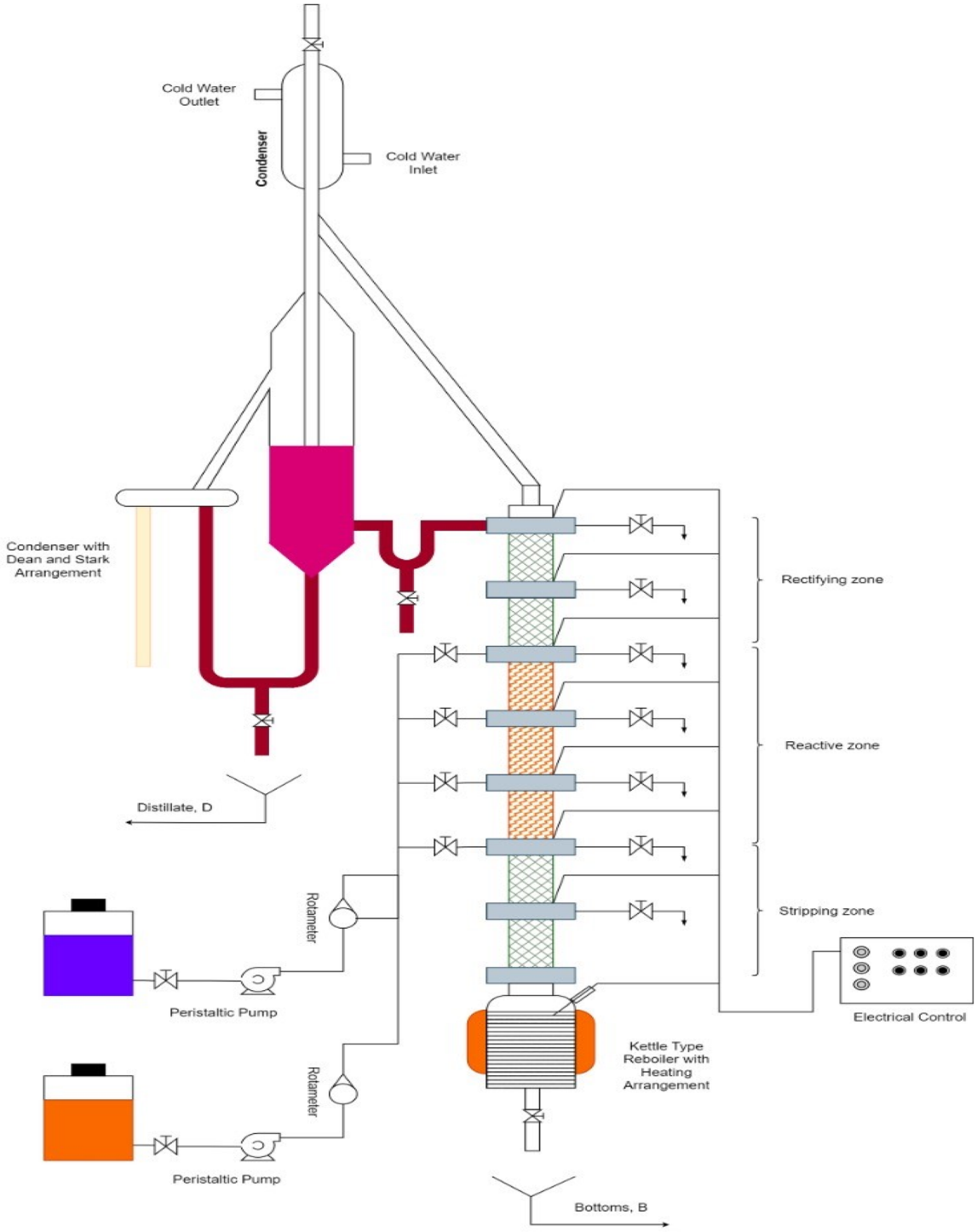

Figure 1: Continuous reactive distillation column [20].

3 Experimental results

The experimental conditions are as follows: solid catalyst: Indion 180; feed location: acetic acid supplied above and methanol is supplied below the reactive zone; feed mole ratio: 1:1, reboiler temperature: 80 °C, reflux raio: 2.0, catalyst amount: 60 g/m, acetic acid feed flow rate: 10.48 g/min, methanol feed flow rate: 5.55 g/min, distillate flow rate: 12.56 g/min and bottoms flow rate: 3.5 g/min.

The overhead product in all the experimental runs was methyl acetate and methanol. The maximum amount in the distillate is methyl acetate and remaining is methanol.

The bottom mixture in the reboiler is major amount of water and little amount of acetic acid.

The acetic acid conversion is calculated as the quantity of acetic acid in distillate and reboiler to the quantity of acetic acid in the feed. The following Eq. (1) is used to calculate the acetic acid conversion in a continuous reactive distillation column.

$$X_A = 1 - \frac{(Bx_{Ab} + Dx_{Ad})}{F_A x_{Af}} \quad (1)$$

where,

x_{Ab} – mole fraction of the acetic acid in the bottoms.

x_{Ad} – mole fraction of the acetic acid in the distillate.

x_{Af} – mole fraction of the acetic acid in the acetic acid feed stream.

B – bottom molar flow rate, mol/min.

D – distillate flow rate, mol/min.

F_A – acetic acid flow rate, mol/min.

Table 1 shows the laboratory reactive distillation column specifications.

Figure 2 show, the composition profile in a reboiler as a function of time throughout the experiment till the steady state condition. Only methanol is present till the 1.5 h of start-up time due to existence of pseudo steady state condition from condenser (top) to reboiler (bottom) of column. After 1.5 h, the feed was started to the column where the methanol fed from below the reactive zone and acetic acid fed above the reactive zone. The reaction between acetic acid and methanol occurs in the reactive zone after contacting with catalyst. From Figure 2, it is observed that, the water concentration is increased from 2 to 12 h and methyl acetate concentration is almost negligible in the reboiler because of high volatility of methyl acetate. The acetic acid concentration is observed as 15 % at 10 h and remains constant from 11 to 12 h as 12 % due to formation of un-reacted high boiling acetic acid (118 °C). Methanol also existed in the reboiler because of excess quantity taken in the reboiler. Compared to acetic acid and methanol only water concentration is maximum under the present experimental conditions.

Figure 3 shows the distillate composition as function of time. Methanol is existed in the column till 1.5 h of operation. When the reaction proceeds in the in reaction zone, the products formed are separated in rectifying and stripping zones. In the distillate, the methyl acetate composition is increasing from 1.5 to 12 h whereas the methanol concentration is decreased due to more formation product in the reaction zone. It is also confirmed from Figure 3, that there is existence of acetic acid and water in the distillate because of low volatility of these components. The methyl acetate concentration was found to be 0.95 mol fraction when the

Table 1: Reactive distillation column specifications [20].

Item	Specification	
Column diameter	50 mm	
Column height	3 m	
Height of the rectifying section	1 m	
Height of the reactive section	1 m	
Height of the stripping section	1 m	
Column operating pressure	1 atm	
Nonreactive zone packing type	HYFLUX (Evergreen Technologies PVT. LTD, India)	
	Packing length	0.5 m
	Number of packing elements	4
	HETP	100 mm
	Material	Stainless steel 316
Reactive zone packing type	Equivalent KATAPAK-S (Abhishek Scientific Company PVT. LTD, India)	
	Packing length	100 mm
	Number of packing elements	10
	Wire thickness	0.25 mm
	Mesh size	0.5 mm
	Corrugation angle	45°
	Corrugated spacing	2 mm
	HETP	100 mm
	Interfacial area	750 m^2/m^3
	Material	Stainless steel 316

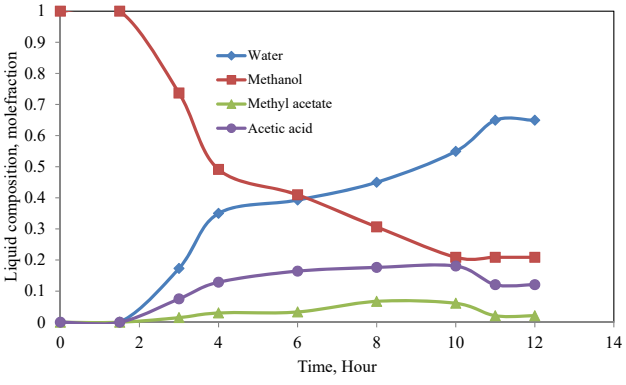

Figure 2: Time-dependent liquid composition profiles in reboiler [20].

system reached steady state, representing a substantial improvement over basic batch reactor equipment [18] (A mole fraction of 0.345). Methanol is present in the distillate due to the low boiling point of methyl acetate.

Figure 4 shows liquid composition profiles in the stripping zone (at 0.5 m height from the reboiler) with respect to time. In the stripping zone, the acetic acid and methyl acetate

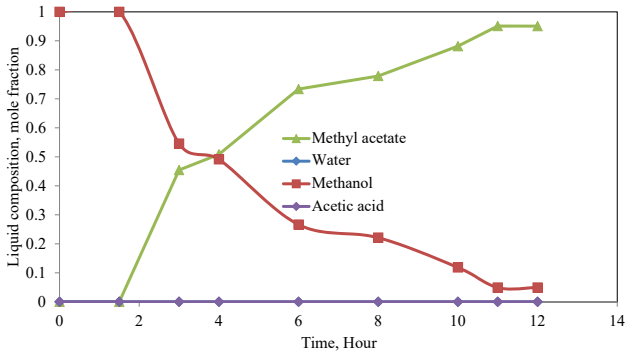

Figure 3: Time-dependent liquid composition profiles in the distillate [20].

concentrations are 0.06 and 0.07 mol fraction at steady state condition i.e. at 12 h. The water composition is constant whereas methanol concentration is decreased from 1 to 0.6445 mol fraction. In the stripping zone only water and methanol are existed due to less separation of methanol from the mixture.

Figure 5 shows the liquid composition profiles in the rectifying section (at 2.5 m height from the reboiler) with respect to time. As shown in Figure 5, the concentration of methyl acetate increases with time. Methanol and methyl acetate concentrations remain unchanged after 10 h of operation. From Figures 1–4, it is suggest that steady state could be achieved at 10 h. The process is continued till two more hours and it is observed that there is no change in concentrations of the components.

3.1 Effect of different operating parameters in the distillate composition

The influence of the total feed flow rate on methyl acetate composition with time in distillate is shown in Figure 6. The

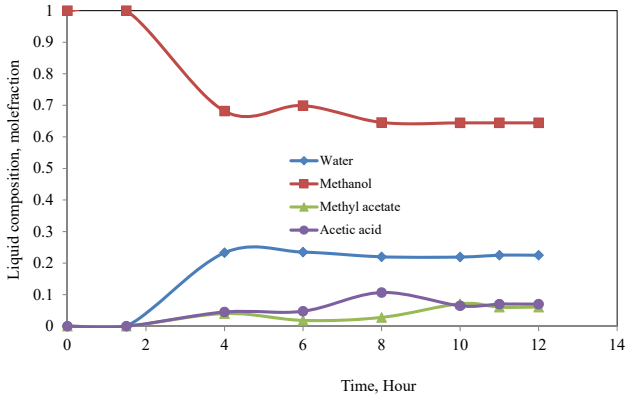

Figure 4: Time-dependent liquid composition profiles instripping section.

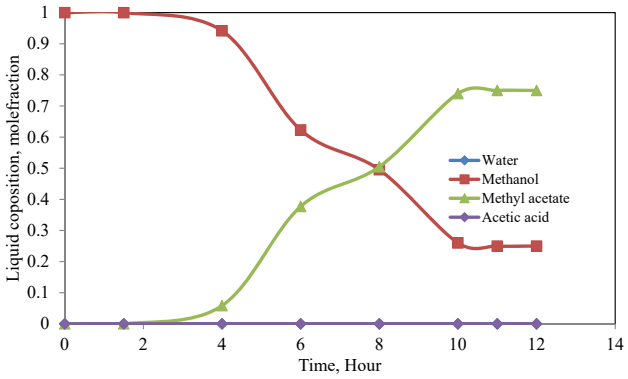

Figure 5: Time dependent liquid composition profiles in the rectifying section.

figure shows that when the overall feed rate increases from 8.6 to 16.03 g/min, the methyl acetate composition increases. However, further increase in total feed flow rates, the composition of methyl acetate decreases. Methyl acetate composition is decreased because the less contact time of the reactants with the catalyst surface or within the catalyst particle. As a result, the optimal total feed flow rate to obtain the higher methyl acetate composition in the distillate is 16.03 g/min.

The influence of reboiler temperature on methyl acetate composition with time in the distillate is shown in Figure 7. The figure shows that the composition of methyl acetate is very low at low reboiler temperatures. At high reboiler temperatures, the rate of methyl acetate composition is initially more and reached steady state composition after 10–12 h of operation. Methyl acetate formation more from 1.5 to 9 h when reboiler temperature is 85 °C compared to 80 °C. After that there is no further increase of methyl acetate at 85 °C. This is due to more temperature allows more vapor

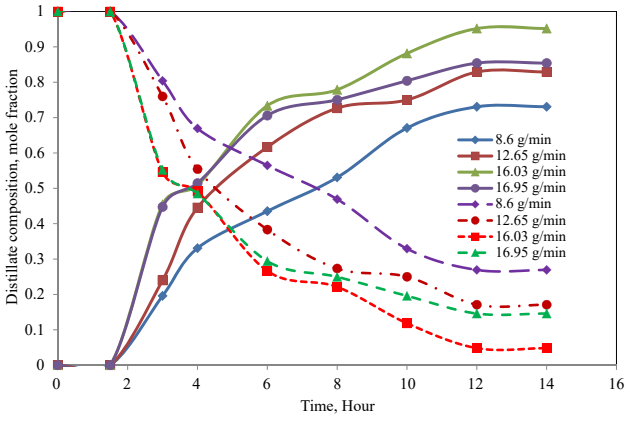

Figure 6: The influence of total feed flow rate on distillate composition (solid lines represents for methyl acetate and dashed lines represents for methanol).

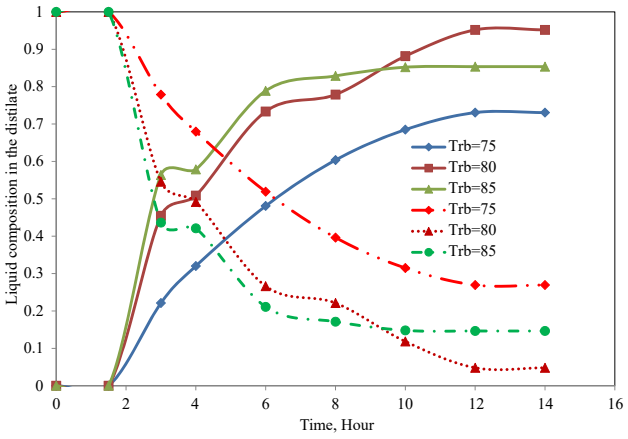

Figure 7: The influence of reboiler temperature on the content of methyl acetate in the distillate (solid lines represent for methyl acetate and dashed lines represent for methanol).

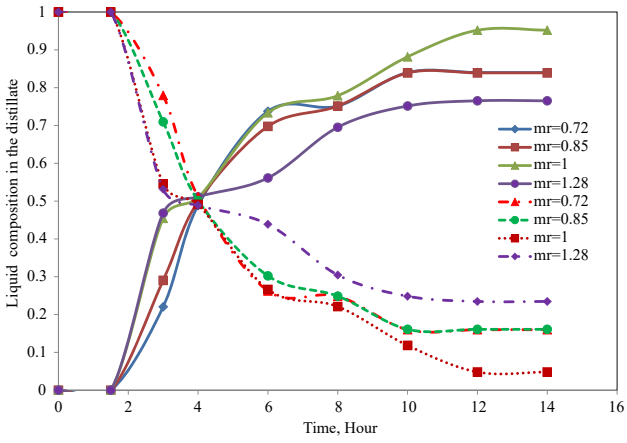

Figure 8: The influence of the molar ratio on the methyl acetate composition of distillate (solid lines represent for methyl acetate and dashed lines represent for methanol).

generation and there could be reversible reaction proceeds by the reaction of methyl acetate and water to form acetic acid and methanol in the reactive zone. At 80 °C, the sufficient contact of reactants with catalyst surface increases the methyl acetate formation in the reactive zone. Hence an optimal temperature could be maintained to achieve high purity of methyl acetate in the distillate. From Figure 7, it is observed that the maximum composition of methyl acetate is achieved at a reboiler temperature of 80 °C.

Figure 8 shows the influence of molar ratio on the methyl acetate composition with time in distillate. When a mole ratio increases from 0.72 to 1, methyl acetate composition is increases. If mole ratio is increased beyond 1, composition of methyl acetate in distillate is decreased due to an excess quantity of the methanol exist in the distillate. Hence excess methanol is not favorable to get the maximum methyl acetate composition in the distillate. At mole ratio of 1, the product mixture separated immediately.

Figure 9 shows, liquid composition profiles in the distillate with time under different reflux ratios of 0.45, 1.5, 2.01, 3.1 and 4.5 respectively. When the reflux ratio is increased from 0.45 to 2, the composition of methyl acetate in the distillate increases, and when the reflux ratio is increased from 2 to 4.5, the composition of methyl acetate in the distillate decreases due to more flow rate into column causes less separation of products in the rectifying and stripping zones. There could be the possibility of reversible reaction to precede products to reactants in presence of catalyst. At a reflux ratio of 2.01 the methyl acetate is maximum of 0.95.

Figure 10 shows, liquid composition profiles in the distillate with time under different catalyst loadings of 40, 60,

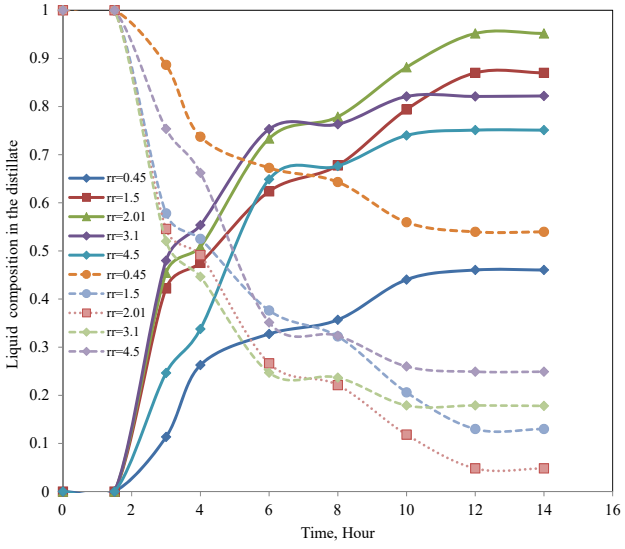

Figure 9: The influence of reflux ratio on the methyl acetate composition in the distillate (solid lines represent for methyl acetate and dashed lines represent for methanol).

80 and 100 g respectively. The methyl acetate composition increases as the catalyst amount/loading increasing from 40 to 100 g/m. In our earlier study [18], from the kinetic investigations, it was observed that as the catalyst amount increases the reaction rate increases. Figure 10, clearly shows, there is drastic change in the methyl acetate mole fraction 40–60 g/m in the reactive zone. Further increase in catalyst loading from 60 to 100 g/m, only marginal improvements in methyl acetate composition. It can be suggested from Figure 10, that 60 g/m catalyst loading is the sufficient for methyl acetate production in reactive distillation.

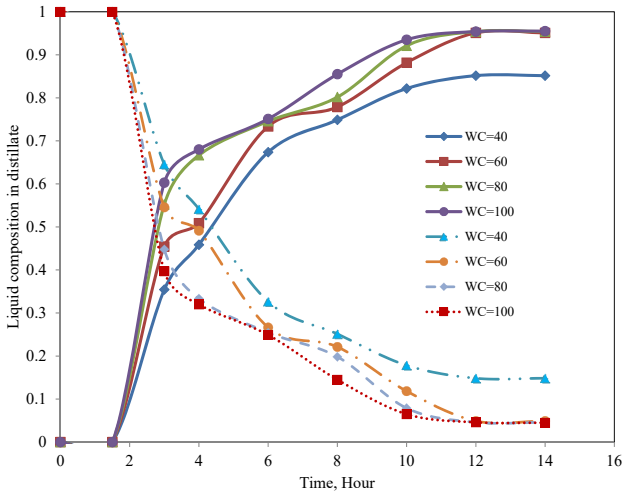

Figure 10: The effect of catalyst quantity/loading on the methyl acetate content of the distillate (solid lines represent for methyl acetate and dashed lines represent for methanol).

4 Conclusions

The production of methyl acetate in reactive distillation has been conducted in presence of an ion exchange resin catalyst from unsteady state to steady state under various operating parameters. The effect of mole ratio, total feed flow rates, reflux ratio, reboiler temperature and catalyst amount is studied on the methyl acetate composition in the distillate. First time, the start-up dynamics from unsteady state to steady state is explained for distillate, reboiler, rectifying and stripping sections. The maximum methyl acetate composition is obtained at 80 °C temperature, 16.03 ml/min feed rates, 1:1 mol ratio, 2.01 reflux ratio and 60 g/m catalyst amount. The present study helps the researches to conduct the experiments for other systems by adopting the same procedure.

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Author contributions: The author has accepted responsibility for the entire content ofthis manuscript and approved its submission.
Competing interests: The author state no conflict of interest.
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Multi Objective Optimization using Non-Dominated Sort Genetic Algorithm with Artificial Neural Network for Reactive Dividing Wall Column

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Abstract—In this study, multi-objective optimization of reactive dividing wall column is presented. Production of methyl acetate from acetic acid and methanol is taken as case study. Machine learning approach is introduced in this work by means of artificial neural network and genetic algorithm. Required data generation, input and output variable fixation to model neural network is done from the sensitivity analysis. Based on the dataset, neural network model is trained by Lavenberg–Marquardt algorithm and predict purity and TAC of column with high accuracy. Further parametric constrained optimization of systems has been done using multi-objective genetic algorithm and set of pareto optimal solution is generated. Based on gray relational analysis, best optimal point found out. After optimization the system gives significant reduction on TAC and enhancement in purity. Results shows reactive dividing wall column reduces total annual cost around 17.77%. All the results in present work is validated with exiting literature and also cross validated with ASPEN plus.

Keywords: reactive distillation, machine learning, optimization, sensitivity analysis

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1. INTRODUCTION

Highly integrated systems known as Reactive Dividing Wall Columns (RDWCs) are capable of performing multi component separations and chemical reactions in the same physical unit. Due to its capacity to give substantial cost and energy savings, Reactive Distillation Columns (RDCs) and Divided Wall Columns (DWCs) become more common in chemical processes [1, 2]. However, RDWCs have not yet been widely accepted. Only in the past ten years has RDWC research been a focus, and tests have shown that the technology is viable from an industrial standpoint [3–10]. A RDWC's general construction is similar to that of a typical dividing wall column. Here feed side of a partition wall, however, is where there is a significant variation. A reactive zone is set up inside the pre fractionator where the feed stream's reactants are converted into the required products. But due to complex behavior and highly non linear nature RDWC [11–14] becomes very difficult to model the system and optimize it. Chemical engineers have used mathematical modeling for understanding and creating chemical processes since last 130 years. In last few years due to availability in data and availability of computational software leads easy introduction of Machine Learning (ML) approaches in chemical engineering. Over the traditional modeling techniques ML had significant advantages [15]. ML models can learn by itself, it can recognize difficult patterns and improves over the time. AI/ML models are made to model very complex non-linear chemical systems [6]. Artificial neurons, which are a set of interconnected units or nodes that loosely resemble the neurons in a biological brain, are the foundation of an ANN. A neural network, also known as an artificial neural network (ANN), is a dynamic system that was artificially formed and is composed of numerous simple computing units connected to one another in specific ways [16–19]. Information can be processed using this system by modifying the correlation between thousands of nodes. The possible relationship between I/P and O/P can be precisely identified and learned using ANN, which can then be used to forecast or increase its efficiency. Given accurate dataset and sufficient neurons in its hidden layer, a two-layer feed-forward network with sigmoid hidden neurons and linear output neurons

Table 1. Kinetics data and process parameters for simulation

Forward reaction	
k	4210
E	8502.91 cal/mole
Backward reaction	
k	930
E	9553.6 cal/mole

Table 2. Column specifications

Specification	Value
Column diameter, mm	50
Column height, m	3
Column operating pressure, atm	1
Number of stages	30
Reflux ratio	2
Reactive stages	10

(fitnet) may arbitrarily well fit multi-dimensional mapping problems. Unless there is not enough memory, scaled conjugate gradient back propagation (trainscg) will be used to train the network instead of the Levenberg–Marquardt back-propagation algorithm (trainlm) [20–22]. ANN can learn complex functional relations for a system from the input and output data of the system. ANN evaluation is much less computationally demanding making them suitable for real time optimization by coupling with any optimization algorithm.

The main objective of the present study is finding of optimal parameters of the reactive divided distillation column by using ANN combined with GA with minimization of capital cost and maximization of purity of methyl acetate.

2. REACTIVE DIVIDING WALL COLUMN (RDWC) SIMULATION

To develop any kind of machine learning model, data used to train that model plays vital role. It is very crucial to collect significant number of data from available literature. So to simplify the process data is generated through ASPEN plus process simulation [23]. To simulate aspen flow sheet required kinetic and process data collected from available literature [24–26].

Acetic acid and methanol react together to form methyl acetate. The reaction scheme can be shown as follows,

$$\underset{\text{Acetic acid}}{CH_3COOH} + \underset{\text{Methanol}}{CH_3OH} \rightleftarrows \underset{\text{Methyl acetate}}{CH_3COOH_3} + \underset{\text{Water}}{H_2O}.$$

The kinetic parameters used in the present study are shown in Table 1. Table 2 shows the reactive distillation column specifications.

The process is simulated using Aspen plus V10 process simulator using two Radfrac columns. The reactive component is located on the left side of the RDWC by keeping partition wall, and the entire normal RD process is integrated into it. At bottom section of dividing wall internal vapor split ratio (α_V) which is ratio of V_s/V is present. In this equation, Vs stands for the flow rate of vapor delivered to the right hand side of separating wall, and V stands for overall flow rate of vapor ascending from the rectifying section. Additionally, α_V is automatically produced during the simulation. In this case of RDWC, there is no liquid divide. Acetic acid and methanol fed to the column with equal flow rate of 25 kmol/hr at 10th and 20th stage respectively and reflux ratio kept at 2. Other kinetic parameters and operating conditions implement as per the available literature.

3. ECONOMIC ANALYSIS

The basic economic foundation for distillation column has been given by following equations [21, 22, 27].

For column

$$\text{Column cost} = 17640(\text{Dia})^{1.066}(\text{Height})^{0.802}. \quad (1)$$

Where diameter and height are in meters.

For condenser

Heat transfer coefficient = 0.852 Kw/m^2 K

Differential temperature = 13.9 K

Condenser area is in m^2

$$\text{Capital cost} = 7296(\text{Condenser area})^{0.65}. \quad (2)$$

For Reboiler

Heat transfer coefficient = 0.568 Kw/m^2 K

Differential temperature = 34.8 K

Reboiler area is in m^2

$$\text{Capital cost} = 7296(\text{Reboiler area})^{0.65}. \quad (3)$$

Energy

Middle pressure steam (11 bar, 457 K = $ 8.22/GJ)

Electricity = $ 16.8/GJ

Refrigerant chilled water at 50C = $ 4.43/GJ

Payback period = 3 years.

$$\text{Capital cost} = \text{Column capiatl cost} + \text{condeser cost} + \text{reboiler cost}. \quad (4)$$

Table 3. Manipulated variables for sensitivity analysis of RDWC

Manipulated variables (base case value)	Varied range
Acetic acid feed temp. (300 K)	298 to 360 K
Methanol feed temp. (300 K)	298 to 360 K
Reflux ratio (2)	1.6 to 2.4
Acetic acid feed flow rate (10 mol/hr)	8.4 to 12.6 (mol/hr)
Methanol feed flow rate (10 mol/hr)	8.4 to 12.6 (mol/hr)
Acetic acid feed stage location (10)	2 to 29
Methanol feed stage location (20)	15 to 29
LIQ. Stream feed stage location (15)	10 to 20

$$\text{Total annual cost} = \frac{\text{Capital cost}}{\text{Payback period}} + \text{Energy cost.} \quad (5)$$

4. SENSITIVITY ANALYSIS

To investigate the effect of manipulated variable on the measured variable sensitivity analysis has been done. For the reactive dividing wall column (RDWC) measured variable and manipulated variable and their base case value and varied range given in Tables 3 and 4.

5. EFFECT OF ACETIC ACID FEED TEMPERATURE

5.1. Effect of Methanol Feed Temperature

From Figs. 1 and 2 it is clearly shown that there is significant effect of feed temperature on methyl acetate purity and TAC both but changing feed temperatures requires preheating that affects the increase in energy cost so that in this case feed temperature is not considered as decision variable to develop ANN model.

5.2. Effect of Reflux Ratio

As reflux ratio increases product purity increases until the reflux ratio value of around 1.9, once it reach that value after that its start decreasing. From the above figure it is evident that changes in reflux ratio have the significant effect on product purity of RDWC. While reflux ratio increases total annual cost of reactive distillation dividing wall column goes on increasing. The reason behind increase in total annual cost is increase in reflux ratio tends to increase in column diameter but in this case study as column diameter kept as constant so its directly affects on the reboiler and condenser duty results in that total annual cost of distillation column increases. So from Fig. 3 it is considered that reflux ratio has significant effect on purity and total annual cost therefore reflux ratio is considered as one of the decision variable in neural network modeling and multi-objective optimization.

5.3. Effect of Acetic Acid Feed Flow Rate

Figure 4 shows effect of change in acetic acid molar flow rate and change in methanol flow rate on the methyl acetate product purity and TAC on the reactive distillation dividing wall column respectively. As feed flow rate increases methyl acetate purity starts increasing. Once flow rate reaches to 0.01 kmol/hr highest purity of 99% achieved and again increasing in acetic acid flow rate purity remains constant and as flow rate increases total annual cost decreases, decrease in TAC is not sudden, it's decreasing gradually. As higher flow rate TAC continue goes on decreasing. From Figs. 4 and 5 it is evident that both feed flow rate should be considered as decision variable for neural network modeling.

5.4. Effect of Methanol Feed Flow Rate

5.4.1. Effect of acetic acid feed location. Figure 6 shows that the effect of acetic acid feed location on Purity and TAC of RDWC. it is clearly shown that at the top of RDWC purity is high and as feed stage location change from top to bottom methyl acetate purity decreases while at top of column at 8th stage TAC is moderate and as its location shifts towards bottom its start decreasing but after 10th stage TAC again starts increasing.

Table 4. Measured variables for sensitivity analysis of RDWC

Measured variables	Base case value
Methyl acetate purity	99%
Total annual cost, $/year	903.542 $/year

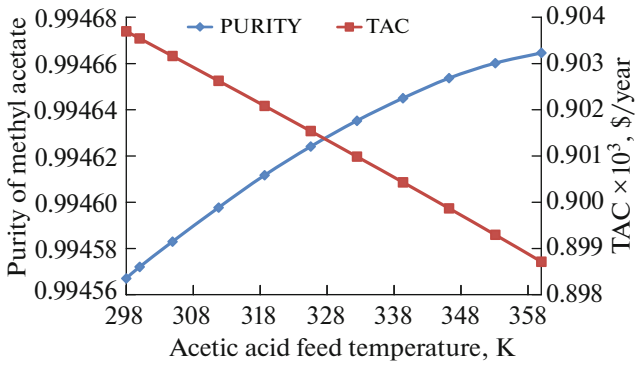

Fig. 1. Effect of acetic acid feed temperature on purity and TAC of RDWC.

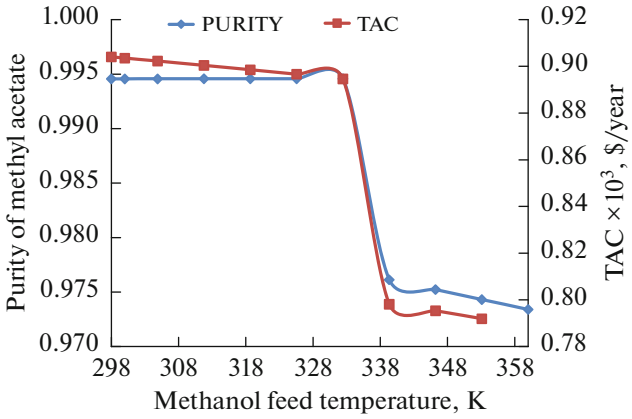

Fig. 2. Effect of methanol feed temperature on purity and TAC of RDWC.

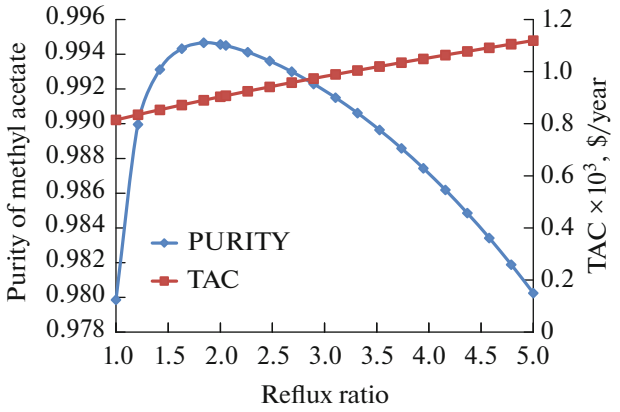

Fig. 3. Effect of reflux ratio on purity and TAC of RDWC.

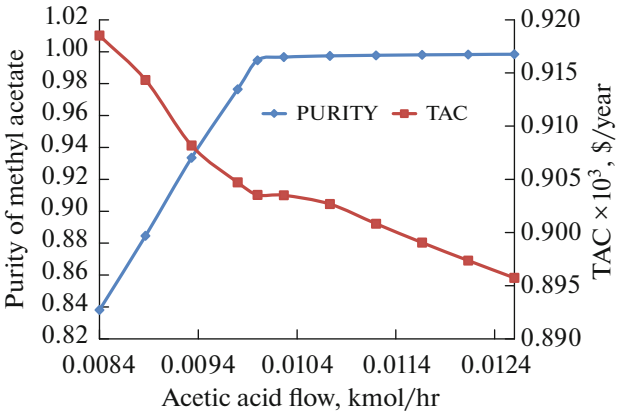

Fig. 4. Effect of acetic acid feed flow rate on purity and TAC of RDWC.

5.4.2. Effect of methanol feed stage location. Figure 7 shows that the effect of methanol feed stage location on Purity and TAC of RDWC. For the methanol feed stage location, sensitivity analysis shows feasible results in aspen plus from 15th stage. As feed stage shifts towards bottom i.e. after 15th stage, purity starts gradually increasing till 21st stage and after that it suddenly falls. Alsochange in methanol feed stage location on total annual cost of reactive distillation dividing wall column. From stage 16th to 21st TAC slowly decreasing and after that it suddenly decreases. Even though feed stage location varying by keeping another location constant there will be the significant change due to height of reactive part, due to this reason feed stage location of acid and methanol should be consider as decision variable in modeling.

5.4.3. Effect of liquid stream feed stage location. Figure 8 shows that the effect of liquid stream feed stage location on Purity and TAC of RDWC. In RDDWC, liquid stream is one of feed coming from side column which represent as divide wall of system. 16 it is clearly seen that varying liquid stream feed location; there is significant effect on product purity and total annual cost. As liquid stream feed location changes purity starts decreasing and TAC starts increasing. Due to this significant effect liquid stream feed location also one of decision variable for modeling of neural network and optimization in case of RDDWC scheme. From the sensitivity analysis all measured variable has been studied. How each and every parameter affects the methyl acetate purity and total annual cost has recognized. From all eight variables studied, both feed flow rates, reflux ratio and all feed stage location has been considered as decision variable for artificial neural network modeling.

5.4.4. ANN topology. ANN analogy flow chart is shown in Fig. 9. From the investigation of sensitivity analysis decision variables are finalized to give as an

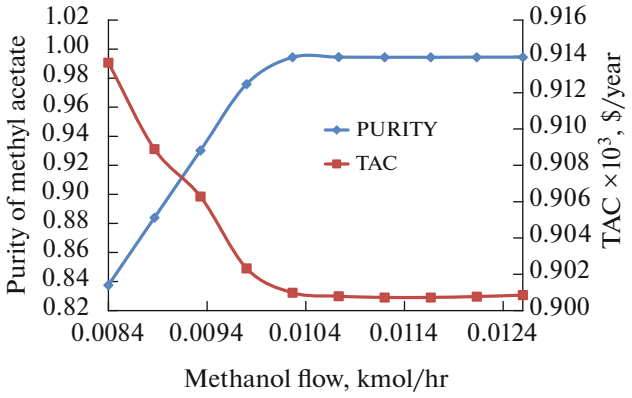

Fig. 5. Effect of methanol feed flow rate on purity and TAC of RDWC.

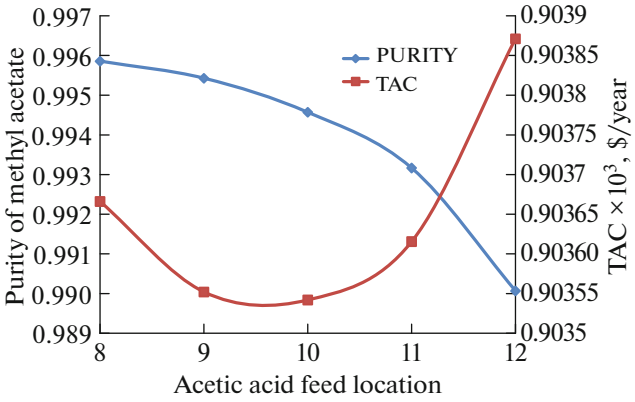

Fig. 6. Effect of acetic acid feed location on purity and TAC of RDWC.

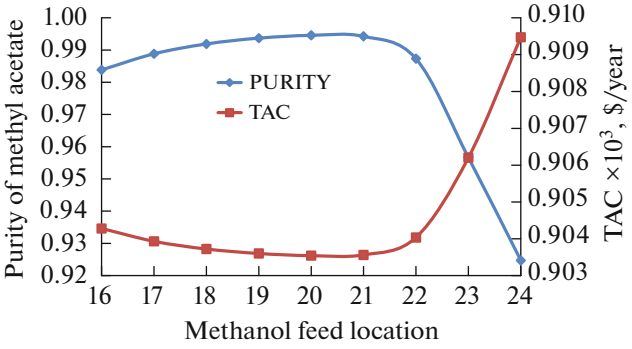

Fig. 7. Effect of methanol feed stage location on purity and TAC of RDWC.

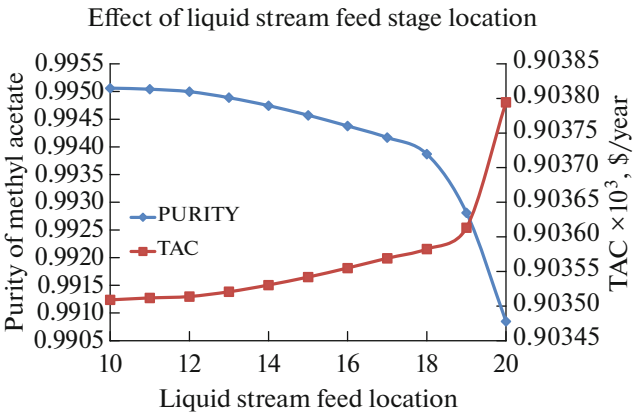

Fig. 8. Effect of liquid stream feed stage location on Purity and TAC of RDWC.

input to ANN and measured variable are considered as output. Data frame was developed by varying all applicable decision variables at once and collected M × N dimensional datasets. Once dataset became ready it is given to ANN toolbox in MATLAB. In this study a multi-layer perception is used in which network are interconnected in such a way that it forms feed-forward arrangement. The no. of hidden layers and neurons is fixed by trial and error method in which best neural network architecture was selected based on mean squared error (MSE) and R^2 value. The Lavenberg Marquardt method which is very commonly based on quasi Newton technique is used for training, testing and validation. To avoid overtraining a cross validation technique is used. Objective of this technique is fixed as split the dataset into 70% training, 15% validation and 15% testing.

From the Table 5 shows MSE and R values for 6 input variable 1 output variable and number of hidden neurons varied from 10 to 80 for purity. As per cross validation 70, 15 and 15% data points were splits into training validation and testing. With hidden neuron 70, ANN gives best performance, low MSE and high R value. And for TAC with 6 inputs, 1 output and number of hidden neurons varied as 10 to 50, as per 70, 15 and 15% splitting 10938 sample for training, 2344 samples for testing and 2344 samples for validation has been taken by neural network. From the figures it is clearly seen that using 45 no. of hidden neurons MSE and R both the values are almost same for training, validation and testing.

5.4.5. Optimization framework. Artificial neural network function to predict purity and total annual cost is used to formulate objective function. Here maximization of product purity and minimization of total annual cost is necessary. Since both the functions are conflicting, also based on decision variables it is clearly seen that mixed integer variables are there, genetic algorithm is a suitable tool to solve the mixed integer optimization problem .Also based on the decision vari-

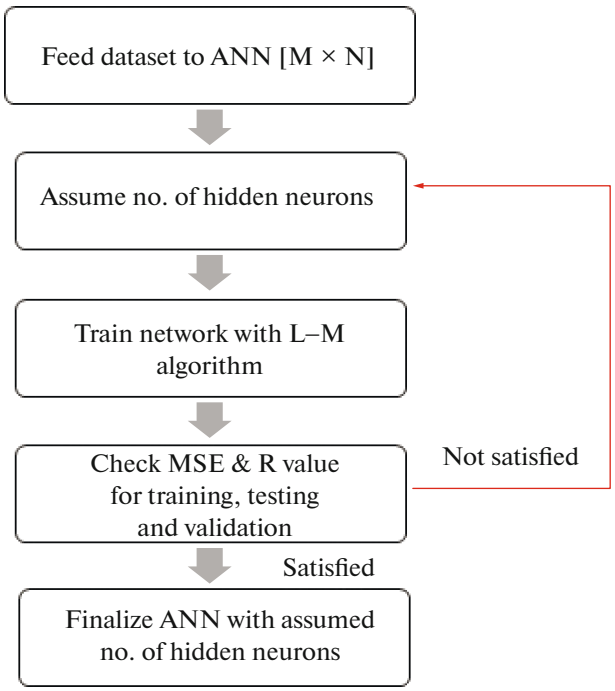

Fig. 9. ANN architecture to model RDWC.

able's bound, constrains are present. Based on overview of problem statement, optimization problem formed as mixed integer constrained optimization.

Objective function can be formulated as [28–34].

Optimize $\{F1(x), F2(x),.....Fk(x)]$

Subject to

$G_n(x) < 0\ n = 0, 1, 2, 3 \ldots n_{\text{inequality}}$

$H_n(x) = 0\ n = 0, 1, 2, 3 \ldots n_{\text{equality}}$

$x_L < x < x_U$ where F is objective function to be maximized or minimized, k is number of objective function, x is vector of decision variables which are continuous or discrete with x_L lower bound and $x_U$upeer bound, G and H are inequality and equality constraints respectively.

Objective function for maximizing methyl acetate purity and minimizing TAC can be formulated as follows,

Maximize Purity (Y_D methyl acetate)

Minimize TAC ($/year)

Subject to.

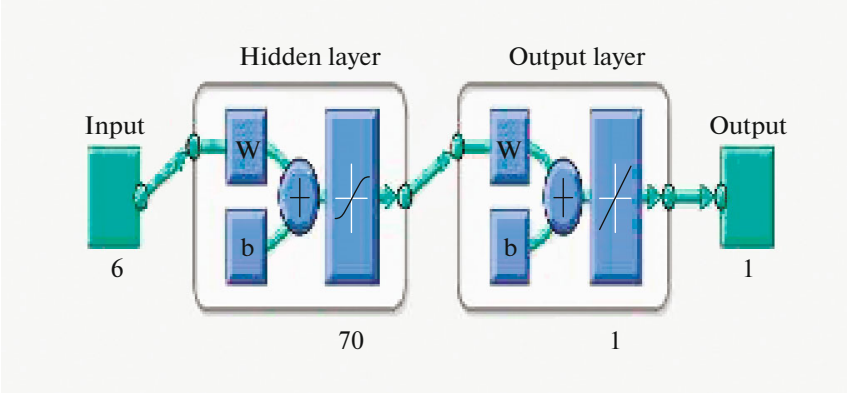

Fig. 10. Finalized ANN model for prediction of RDWC Purity.

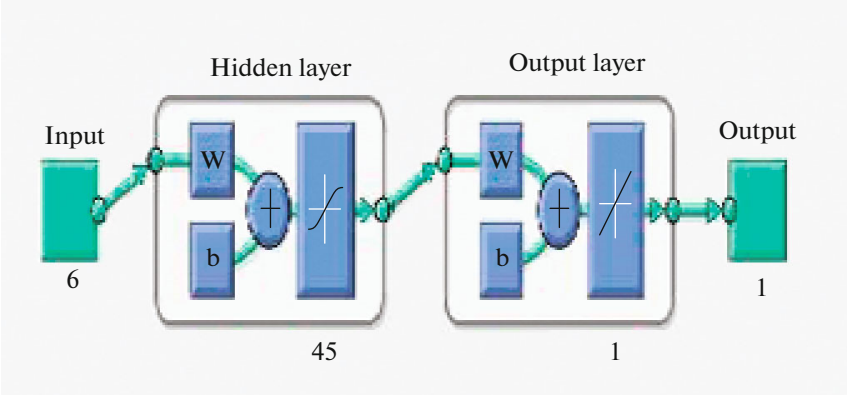

Fig. 11. Finalized ANN model for prediction of RDWC TAC.

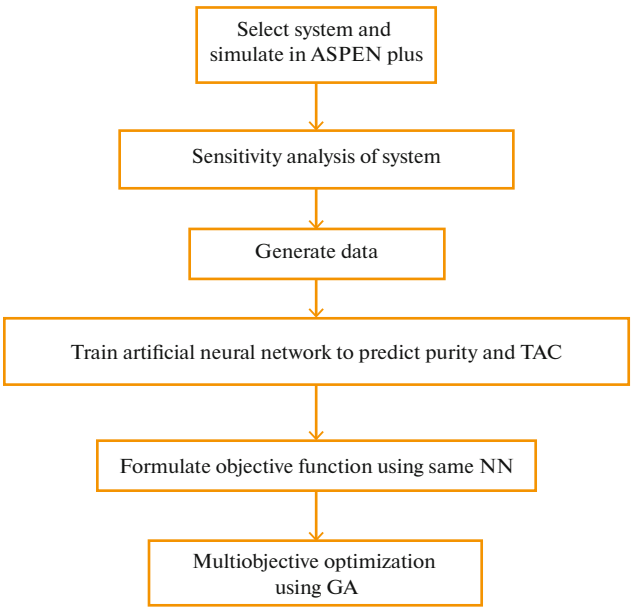

Fig. 12. Methodology flowchart.

8 mol/hr < acetic acid flow rate< 14 mol/hr
8 mol/hr < methanol flow rate< 14 mol/hr
1 < RR < 4
8 < acetic acid feed stage location < 12
16 < methanol feed location < 25
10 < Liquid stream feed location < 20

From Fig. 13 represents pareto optimal solution at 300 initial population and 300 maximum generation values. Detailed observation of plots shows that minimum value of total annual cost will be in between 0.742×10^3 to 0.743×10^3 \$/year and maximum value of purity will be in the range of 0.994 to 0.999. At the value of initial population 300 and 300 maximum generations, smooth paraeto curve got. Still to find out best of best optimal solution further analysis has to be done which will be discussed in GRA.

5.4.6. Gray relational analysis (GRA). This is very simplest and efficient method to find out best optimal point from pareto optimal solution. This analysis algorithm based on gray relational coefficient and concept of data normalization, evaluate GRC and give ranking [17, 35, 36].

Step 1: Data normalization has been done on the basis of larger the better and smaller the better for maxima and minima respectively.

$$\text{norm.}Pij = \frac{Pij - \min Pij}{\max Pij - \min Pij},$$

$$\text{norm.}Pij = \frac{\max Pij - Pij}{\max Pij - \min Pij}.$$

Step 2: Evaluate ref. network point.

$$Pj = \max Pij.$$

Step 3: Diff. between Pj and Pij

$$\Delta Qij = |Pj - Pij|.$$

Step 4: Evaluate gray GRC

Table 5. Finding optimal number of hidden neurons

No. of hidden neurons	MSE			*R*		
for purity	Training	Validation	Testing	Training	Validation	Testing
10	2.87743e-4	3.54567e-4	7.9199e-4	9.8374e-1	9.80682e-1	9.57861e-1
20	3.34771e-4	1.87598e-4	1.82865e-4	9.81488e-1	9.89359e-1	9.89825e-1
30	2.45700e-4	9.98900e-5	9.84701e-5	9.86468e-1	9.94238e-1	9.94584e-1
40	2.41075e-4	1.59724e-4	1.06237e-4	9.86730e-1	9.91176e-1	9.93881e-1
50	1.21633e-4	3.77119e-4	3.11541e-4	9.93261e-1	9.78913e-1	9.92895e-1
60	2.47223e-4	8.39313e-5	7.42488e-5	9.86365e-1	9.95332e-1	9.95814e-1
70	**1.65756e-4**	**2.96697e-4**	**1.61943e-4**	**9.90812e-1**	**9.83402e-1**	**9.91149e-1**
80	1.43596e-4	5.46988e-5	9.74427e-4	9.92056e-1	9.96970e-1	9.47050e-1
For TAC	Training	Validation	Testing	Training	Validation	Testing
10	3.38947e-6	2.27397e-6	6.30481e-6	9.99844e-1	9.99896e-1	9.99702e-1
20	3.12323e-6	1.19529e-6	1.26470e-6	9.99856e-1	9.99942e-1	9.99942e-1
30	1.49878e-6	6.21024e-7	5.80164e-6	9.99931e-1	9.99971e-1	9.99734e-1
40	1.19356e-6	5.61434e-6	7.48955e-7	9.99944e-1	9.99745e-1	9.99965e-1
50	2.56928e-6	9.43602e-7	1.00565e-6	9.99880e-1	9.99957e-1	9.99954e-1
45	**2.60796e-6**	**6.84561e-7**	**7.29532e-7**	**9.99886e-1**	**9.99970e-1**	**9.99967e-1**

Table 6. Governing options for genetic algorithm

Parameter name	Value
Number of decision variable	6
Number of objective	2
Population size	Varied from 50 to 300
Maximum generations	Varied from 50 to 300
Selection function	Tournament
Crossover method	Two points
Crossover probability	0.95
Mutation function	Constraint dependent

Table 7. From GRA, best solution for objective function

Max purity	Min TAC × 10^3, \$/year	Acetic acid flow rate, mol/hr	Methanol flow rate, mol/hr	Reflux ratio	Acetic acid feed stage location	Methanol feed stage location	LIQ. Stream feed stage location
0.99982	0.742931	11.832	13.79	1.00775	12	19	16

Table 8. Result comparison between conventional and optimized RDDWC

Parameter	Conventional RDDWC	Optimized RDDWC
Acetic acid feed flow, mol/hr	10	11.832
Methanol feed flow, mol/hr	10	13.79
Reflux ratio	2	1.0075
Acetic acid feed stage location	10	12
Methanol feed stage location	20	19
LIQ stream feed stage location	15	16
Methyl acetate purity	0.99	0.99982
TAC, \$/year	903.542	742.931
% reduction in TAC	–	17.77%

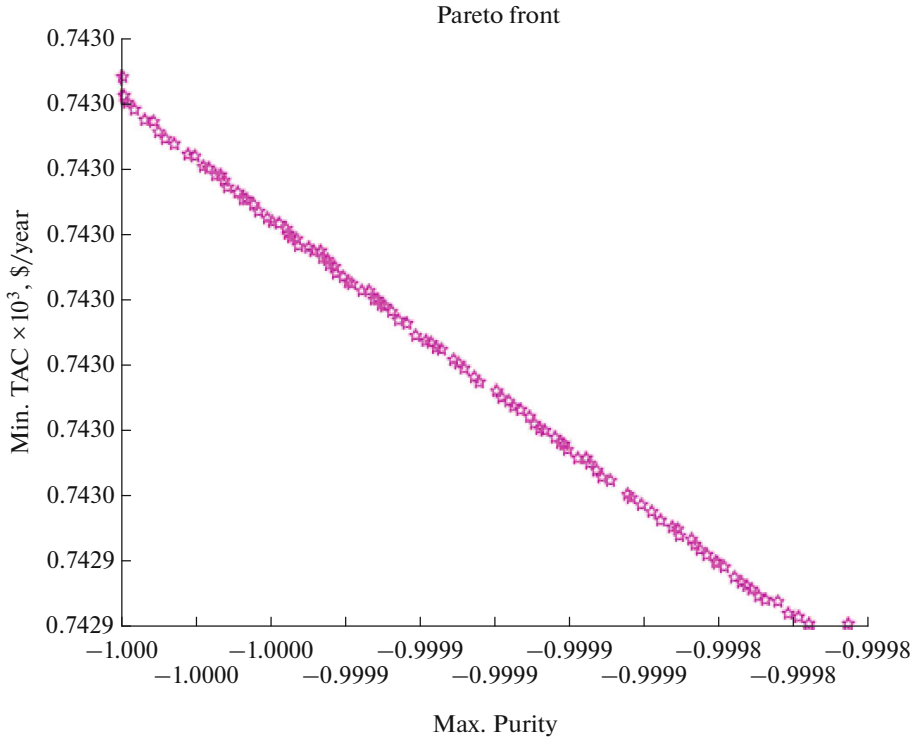

Fig. 13. Pareto plot for 300 initial population and maximum generations of 300.

$$\mathrm{GRC} = \frac{1}{m}\sum_{j=1}^{n}\frac{\Delta\min + \Delta\max}{\Delta Qij + \Delta\max}.$$

Step 5: give the ranking to the GRC and whoever has rank 1, the corresponding values are the best optimal solution which is desirable.

All the points on pareto plots are best optimal solutions for the objective function. A process engineer can take any of point among these as per the requirement but to it is necessary to find out a best optimal solution from all optimal points using Grey Relational Analysis.

6. CONCLUSIONS

In this work artificial neural network club with genetic algorithm has been used to find out optimal values of operating parameters by maximizing purity and minimizing total annual cost of reactive dividing wall column. Since purity and TAC both are conflicting to each other, genetic algorithm is perfectly suits for multi-objective optimization. After successful generation of dataset using sensitivity, ANN accurately predicts purity and TAC for the systems. The same ANN function used as a fitness function for GA and then to find out best optimal points GRA was used. After optimization RDW column gives 17.77% of savings in TAC over conventional cost with highest purity of 99.9%. Since column structure kept constant as only parametric optimization has been done, column capital cost remain constant so that only reboiler cost, condenser cost and energy cost reflecting in calculation of TAC. Considering this fact, the saving in TAC shown by RDWC it is concluded that there is significant amount of energy saved by reactive dividing wall column.

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CONFLICT OF INTEREST

The authors of this work declare that they have no conflicts of interest.

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Biodiesel production from blended feedstocks and by-product utilization for achieving sustainability

Sadia Husaini, Akshara Kadire, Raj Kumar Verma, Madhuri Pydimalla

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Abstract

Rapid population development has increased the need for fossil fuels, which has prompted a search for renewable alternatives to lessen the impact on the environment and resource shortages. Biofuels, specifically biodiesel, have surfaced as a potentially viable solution to these challenges while also contributing to environmental sanitation. However, biodiesel production faces difficulties in terms of the availability of raw materials. To overcome these challenges, the concept of using mixed oils has gained prominence, reducing reliance on a single oil source. Enhancing the quality of biodiesel through the refinement of composite feedstock ratios is the principal aim of this research. In this study, Biodiesel was produced via a base-catalyzed transesterification process from a hybrid oil mixture of Jatropha and Karanja, utilizing different molar ratios (60:40 and 70:30). The outcomes of the experiment demonstrated a biodiesel yield of 81% under specific reaction conditions: temperature of 70°C, reaction time of 2h, and an alcohol-to-oil ratio of 8:1. The produced biodiesel underwent comprehensive characterization, including analysis of Cloud point, Specific gravity, Pour point, Acid value, Moisture content, Flash point, Fire point and Density. These properties were

compared to ASTM standards to assess the potential of biodiesel as a viable diesel substitute. The 60:40 and 70:30 ratios passed the 27/3 test and had FFA% and acid values within ASTM limits. Both mixtures had pour points within ASTM limits of −15 to 10°C and flash points higher than the minimum requirement of 130. Both feedstock ratios considered, 60:40 and 70:30 (Jatropha: Karanja), exhibited significant compliance with the ASTM standards. Comparatively, the 70:30 mixture had the highest yield (85.26%) and showed better results overall such as having lower cloud and pour points, 2°C and −3°C compared to the 60:40 ratio having 4°C and −2°C respectively. Moreover, the by-product of the process was utilized in the production of soap, exemplifying a zero-waste approach in biodiesel production and promoting sustainability.

Introduction

The significant growth in industry, transportation, urbanization, and rapid population expansion contribute to the substantial energy demand [1]. It is estimated that by 2050, fossil fuels could account for up to 65% of global energy consumption. Presently, energy generation heavily relies on non-renewable fossil fuels. These fossil fuels are finite resources that will eventually be depleted. Furthermore, the combustion of fossil fuels leads to the release of greenhouse gas emissions, which are a major contributor to environmental degradation and global warming [2]. Investigating substitute fuels that lessen our need for imported crude oil and support long-term environmental preservation is now essential. Renewable energy resources (solar, wind, geothermal, hydro, biomass, etc.) are increasingly being advocated throughout the globe as a means to lessen reliance on fossil fuels and thereby decrease emissions of dangerous greenhouse gases. Bioenergy derived from biomass is seen as a replacement for fossil fuels since gasoline and diesel are the liquid fuels most commonly utilized. Biofuels such as bioethanol, biodiesel, and biogas overcome the highlighted difficulties with a cleaner environment and several other advantages [3]. Due to its comparable physicochemical qualities to petroleum diesel, biodiesel has received significant interest in recent years as a biofuel replacement.

Biodiesel is a renewable, non-toxic, carbon–neutral, and eco-friendly energy source that may be used in the current engine without requiring significant modifications [4], [5]. Utilizing biodiesel is risk-free for engines since it increases combustion efficiency, decreases emissions, and improves lubricity without adding sulfur or oxygen to the fuel molecules [6], [7]. Chemically, biodiesel is known as fatty acid methyl esters (FAMEs) [8].

Following the COVID-19 outbreak, it is estimated that the worldwide market for biodiesel will increase at a CAGR of 4.6% from 2017 to 2026, reaching a revised value of $40.2 billion US. According to Agrarmarkt Informations-Gesellschaft, the demand for diesel increased by 1.6% to 15.15 million tonnes in 2021–2022. The average biodiesel/HVO

inclusion rate from January to June 2022 was 7.5%. Europe has the biggest biodiesel market in the world. However, it is anticipated that Europe will grow at a relatively moderate CAGR in terms of volume. This is a consequence of the saturation of the European biodiesel market. Asia-Pacific is the region with the highest anticipated growth rate.

Biodiesel is produced by a chemical process known as transesterification, which includes modifying the chemical characteristics of vegetable oil with methanol [9]. Triglycerides (fats) are the primary component of oil feedstock. The process of transesterification, in which lipids react with alcohol, is utilized to produce biodiesel. Triglycerides, which are the fundamental components of lipids (oils/fats), are composed of a single glycerol and three fatty acids. As a result, the alcoholysis process of lipids produces biodiesel, which is composed of monoalkyl esters, in addition to glycerol as a byproduct. Ethanol and methanol are the most often used alcohols because their chain lengths are the shortest and they are less costly than other alcohols. Both alcohols, but mostly methanol because of their shorter chain length, swiftly react with triglyceride present in feedstock and easily dissolve in it. To favor the desired outcome, a greater quantity of methanol is required due to the bidirectional nature of transesterification. The by-product glycerol may be used to produce soap. The use of an alkaline, acidic, or biological catalyst is feasible. Base-catalyzed transesterification is four thousand times quicker than acid-catalyzed transesterification [10]. This biodiesel meets the requirements of ASTM D6751 and EN 14214. Transesterification produced fuels with increased cetane ratings, lower emissions, and improved combustion efficiency. The fundamental drawback of this procedure is that it takes at least double the stoichiometric quantity of methanol. To generate biodiesel on an industrial scale, it is necessary to establish ideal transesterification conditions and catalysts that are effective, economical, and ecologically benign.

The availability of oil resources (eg: animal and fish fat, edible and nonedible oils, yellow grease, and algae) poses a barrier to biodiesel manufacturing. According to an estimate that 60–90% of the cost of biodiesel production is attributable to the cost of feedstock oils, the production of biodiesel from edible oils is hampered by food versus fuel issues. Thus, the manufacture of biodiesel from edible oils is rendered difficult due to the divergence of resources between meeting food demands and fueling transportation. In addition, non-edible oils such as jatropha curcas, Pongamia pinnata, Calophyllum inophyllum, and ceiba pentandra, etc., as second-generation seed oils, offer the benefits of greater availability, biodegradability, renewability, and liquid mobility, with no competition from food oils [11]. However, these oils are difficult to cultivate due to their high viscosity, high acidity, poor volatility, limited yield, and enormous acreage requirements [12]. High acid-value oil necessitates the esterification process to reduce the acid value to below 2 mg KOH/g before the transesterification process, which raises

the total cost of biodiesel owing to the added time and expense of the esterification process [13]. The global accessibility of third-generation microalgal resources is nevertheless in the first phase of advancement.

The ubiquitous utilization of edible and non-edible oils in biodiesel production is impeded by a multitude of obstacles. The challenges include the exorbitant expense of feedstock oil, inadequate quality standards, competition from food sources, and restricted availability for biodiesel production on a large scale. To solve these obstacles, scholars from throughout the world have proposed many approaches. However, oil mixing before transesterification was suggested as one of the viable approaches for increasing fuel quality effectively and at a low cost [14].

The quest for alternatives to edible oil for biodiesel production has led to the use of non-edible oils, such as Jatropha, Karanja, Linseed, and Palm oil, among others. Compared to food oils, it has been found as a more sustainable and potential biodiesel source. The hydroxyl value of jatropha oil varies between 4 and 20 mg KOH/g. Jatropha oil-based biodiesel is sulfur-free and has excellent lubricating properties, resulting in reduced wear when in contact with metal surfaces. It has minimal quantities of phosphorus and sulfur, therefore sulfur oxide (SOx) emissions are insignificant [15], [16]. The kernel of the Karanja seed is said to contain 30–40% oil. 900 to 9,000 kg of Karanja oil may be produced per acre. It is one of the prospective oils, with an annual output of 1,350 million tonnes, but only 6% is exploited [17]. According to S K Karmee (2004) et al., Karanja oil emits less toxic chemicals and is less costly than jatropha oil [18].

Section snippets

Materials

Jatropha oil and Karanja oil, both with a purity level of 98.5% were procured from Paritosh Herbals, Dehradun, India. The other essential chemicals including methanol, isopropyl alcohol, and potassium hydroxide pellets, all of which are of analytical grade, were sourced from Hi Media Pvt. Ltd., India. …

Methods

Second-generation feedstock was used to eliminate the food vs fuel controversy. For the selection of the best feedstock, we must consider several criteria as explained in Fig. 1. To begin, it is …

Results and discussions

The evaluated characteristics of the produced biodiesel are reported in Table 1. Furthermore, other significant factors that define the quality of fuels were tested in the laboratory and reported in the subsequent section [21]. Moreover, the findings were compared to the respective biodiesel standard (ASTM D 6751) limit. …

Making soap from glycerin

The glycerine by-product acquired during the transesterification process was transferred into a 250ml conical flask subsequent to its collection and weighing, where methanol was extracted by heating the substance on a hot plate. 3g of NaOH was weighed and added to water at 32°C. This mixture was then stirred until NaOH was completely dissolved in water. In a separate beaker, 35g of glycerine (by-product) was heated to around 40°C on a hot plate. The prepared aqueous NaOH was slowly added …

Conclusions

Amid the growing prominence of eco-friendly and economically viable methods for biodiesel production, recent research has substantiated that blending non-edible oils, specifically Jatropha and Karanja, in varying molar ratios (60:40 and 70:30) using base-catalyzed transesterification holds great promise for large-scale biodiesel production. The experimental results reveal that both the 60:40 and 70:30 ratios met the 27/3 test requirements, fell within the acceptable ranges for Free Fatty Acid …

CRediT authorship contribution statement

Sadia Husaini: Writing – original draft, Investigation, Data curation. **Akshara Kadire:** Writing – original draft, Investigation. **Raj Kumar Verma:** Writing – review & editing, Investigation, Conceptualization. **Madhuri Pydimalla:** Writing – review & editing, Supervision, Resources, Conceptualization. …

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. …

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ARTICLE | March 19, 2024

Design of Aluminum Doped ZnO/Phenyl-C-Butyric Acid Methyl Ester/Tungsten Disulfide (AZO/PCBM/WS_2) Heterojunction-Based Device for Applications in Solar Cells and Broadband Self-Powered Photodetectors

Rupam Sinha*

Langmuir
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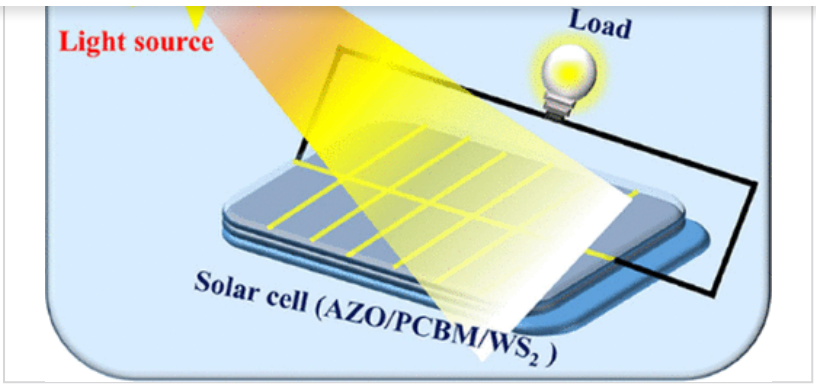

The domain related to the use of renewable energy is showing high interest among the researchers in the current days, and light energy can be considered as one of such. Solar cells are the kind of devices that use light energy in an efficient way to generate electricity. Hence, designing and developing a solar cell requires meticulous attention to get an optimum output. This work focuses on designing and optimization of aluminum dope ZnO/phenyl-C-butyric acid methyl ester/tungsten disulfide (AZO/PCBM/WS_2) heterojunction-based device for applications in solar cells. Moreover, considering the high demand of optoelectronics like photodetectors, this work also uncovers the capabilities of the device in the applications of broadband self-powered photodetectors. The optimized values of several parameters of the device such as the thickness and doping density of the WS_2 layer, the defect density of the WS_2 layer, and the interface PCBM/WS_2 were 2 μm, 10^{17} cm^{-3}, 10^{14} cm^{-3}, and 10^{10} cm^{-2}, respectively. These optimal conditions facilitated in obtaining fill factor and efficiency values of 84.78 and 23.92%, respectively. Further, the photodetection performance was evaluated with the parameters like responsivity and detectivity. The maximum calculated responsivity of the device at 0 V bias was 0.63 A/W at 880 nm, whereas the maximum detectivity was 1.54 × 10^{13} Jones. This study also extensively focuses on the in-depth understanding of the physics associated with the movement of the charge carriers under the illuminated conditions by studying the band diagrams and the electric fields of the heterojunctions at various conditions.

Subjects

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Supporting Information

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Design of Aluminum Doped ZnO/Phenyl-C-Butyric Acid Methyl Ester/Tungsten Disulfide ($AZO/PCBM/WS_2$) Heterojunction-Based Device for Applications in Solar Cells and Broadband Self-Powered Photodetectors

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Experimental Interfacial Reconstruction and Mass Transfer Modelling of a Slug Bubble During Co-current Flow in a Millimetric Tube

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Fluid Mechanics and Fluid Power, Volume 5

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Abstract

Mass transfer during the gas liquid interactions in a monolith reactor has been an area of paramount importance due to its prevalence in process intensification. The present study experimentally investigates the mass transfer from slug bubble train in a glass tube by

using the colorimetric method and a high-speed camera. An oxygen sensitive dye resazurin is used with the pure oxygen cap/slug bubble train for the current study. An in-house code has been developed for image thresholding, interface detection, bubble mask generation, and concentration measurement. It is investigated that the overall mass transfer coefficient increases with the gas superficial velocity. The role of the Taylor recirculation vortices in the mass transfer enhancement has been observed from the radial concentration profile.

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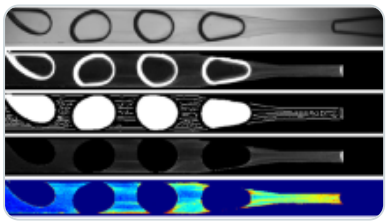

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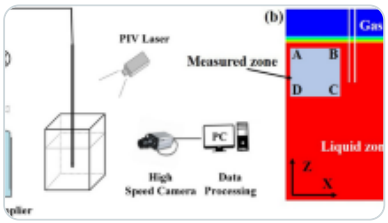

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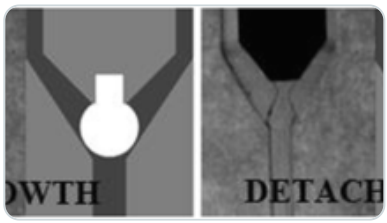

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Abbreviations

d: Tube diameter (m)

U_l: Liquid superficial velocity (m s^{-1})

U_g: Gas superficial velocity (m s^{-1})

D_L: Diffusivity of Oxygen (m^2 s^{-1})

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Optimization of value-added products using response surface methodology from the HDPE waste plastic by thermal cracking

Ganesh Botla [a], Praveen Barmavatu [b], Michael Pohorely [c], Michal Jeremias [d], Vineet Singh Sikarwar [c d]

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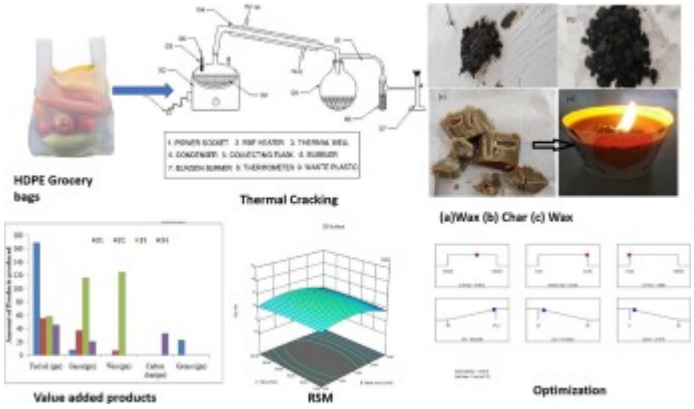
Highlights

- Catalytic conversion of waste grocery bags into value added products by thermal cracking.
- Deployment of bentonite catalyst to produce fuel oil, wax, grease and charcoal without any residues.
- Optimization of process parameters with response surface methodology via CCD method.
- Characterization of produced fuel oil is close to the commercial fuels.

Abstract

The current research aims at the thermal degradation of waste plastic in the presence of bentonite solid catalyst to produce value added products such as fuel oil, gas and charcoal. The thermal cracking of High-Density Polyethylene plastic produces the liquid fuel with conversion around 84.46% with the characteristics: heating value 35.5 MJ/Kg, density 0.749 g/cc, viscosity 1.43 cSt, a boiling point 200 °C and flash point 16 °C. The response surface methodology using the central composite design (CCD) method have been investigated to evaluate the effect of independent variables such as heating rate, temperature, time of operation on the production of value-added products. The optimal operating values for temperature, heating rate and batch time are 473.74 K, 24.9 °C/min and 159.90 min respectively. At the optimal operating conditions, the value-added products produced are fuel oil 91.16%, gaseous products 8% and solids 2%. The experimental results were best fitted with quadratic polynomial model with the appreciable regression coefficient using the response surface method of analysis.

Graphical abstract



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Introduction

In recent years, plastics are part of the human activities in day-to-day life; the extensive usage of plastics creates a huge disposal and environmental problems. The burning and land filling leads to many environmental problems, instead it can be used to produce the value-added products, since the waste plastics contains the hydrocarbons. The management of plastic waste are challenging task that impacts a lot in terms of health and environment. To address the rising of plastic wastes, multiple solutions have been proposed which include reduction, reuse, decomposition, energy recovery and recycling. The favorable solutions are recycling, regenerating, and utilizing of waste plastic is research topic in the current scenario [1], [2], [3], [4], [5], [6]. The methods such as

recycling paid more attention towards the nation's circular economy. Only limited percentage of the used plastic is recycled, the remaining is sent to burnt and landfills. The energy recovery solutions such as thermal cracking and pyrolysis, gasification is receiving more attention nowadays as alternative methods of plastic waste recycling [7], [8], [9], [10], [11], [12]. Thermal cracking of waste plastic is considered as most prominent route for the waste plastic due to its simplicity of conversion into low molecular weight hydrocarbon products which can be used as feed stocks in developing circular economy. The study of effect of process variables such as temperature, residence time, type of plastics, pressure, size of plastics, type of reactor and catalyst on product distribution is most important during pyrolysis process [13], [14], [15], [16], [17], [18].

Many plastics are derived from the fossil resources, which are widely used feed stocks and energy sources to produce different useful products. Conversion of used and unrecyclable plastic into useful hydrocarbons could be environmentally feasible solution for the circular economy. Solid plastic waste mainly consists of high-density polyethylene, low-density polyethylene, polypropylene, polystyrene, polyethylene terephthalate and polyvinyl chloride, etc. Polyethene accounts for about 40% of the solid plastic waste in the total waste stream generating in urban environments [19]. Polyethylene is the third largest waste stream produced among the total solid waste generated across the globe [20], hence it can be considered as the major source to produce valuable products from the waste.

HDPE is a linear and crystalline structured polymer. The main chain molecules regularly line up with side chain molecules. Hence, the longer the main chain greater the molecular weight, stronger the intermolecular forces and temperature resistance is more compared with the light density polyethylene, because of crystalline nature and size distribution of crystalline regions influences the cracking resistance. The products generated from HDPE thermal cracking are mainly includes liquid hydrocarbons apart from the gaseous and solid products, which may be directly used as fuel or upgraded to value added chemical feedstock [21], [22]. The thermal cracking is the process of breaking of the long chain HDPE waste plastic into small hydrocarbons; hence it going to be a viable solution with great potential [23], [24], [25]. Thermal cracking is the process which converts the waste plastic into liquid fuel oil, solid residue (wax and char) and hydrocarbon gases at moderate to high temperature range [26], [27].

Conversion of waste plastic in to value added products mainly dependents on the key process parameters which may influence the production of final products such as fuel oil, gases, and solid products such as wax and char. Tejasvi Ravi and Suriapparao[28] reviewed the role of process parameters on the production of value-added products by thermo-chemical conversion of biomass and plastics into useful products and they reviewed the role of process parameters feed stock size, heating rate, reaction

temperature, residence time, feedstock particle size, and type ofreactor. The thermal cracking of waste plastic is mainly influenced by the parameters such as temperature, type of reactor, type of the plastic and its composition, heating rate, residence time and catalyst.

Plastic waste mainly contains hydrocarbons along with other pollutants such as sulphur, nitrogen and contaminants during their handling. The catalysts selection is a crucial step in the plastic degradation. The modification of catalyst has been under consideration for several years to the efficiency of the process. Nizami et al. [29] reviewed the list of probable catalysts which includes the red mud, ZSM, FCC, HZSM-5, Y-Zeolite, Fe_2O3, Al_2O_3, $Ca(OH)_2$ and natural Zeolites, etc. have been used for the conversion of plastics into value added products. The presence of catalyst has been improved the conversion, the lighter fractions and decreases the energy requirements. In recent years, heterogeneous clay catalysts have been receiving lot of attention because of their practical usage and huge application as green catalyst [30].

The present work aims to find the optimum operating conditions for yield of waste plastic oil from HDPE waste plastic covers using a solid catalyst in a batch reactor. Many studies reported the methods to maximize the liquid fuel from waste plastic for the pyrolysis process but only few studies reported the optimization of process parameters with less accurate parameters. No accurate optimization studies had been developed on the parameters affecting the thermal cracking of HDPE waste plastic to become cost-effective and efficient. The objective of this work is producing the maximum quantity of fuel oil with minimum useful residue by thermal cracking of HDPE waste plastic using the bentonite catalyst and to find the optimum operating parameters to produce the maximum quantity of fuel oil.

The various parameters considered to produce value-added products from solid plastic are temperature, heating rate, batch time, type of plastic, feed size, type of reactor, type of catalysts. Among the various process parameters heating rate is the important parameters which affect the thermal cracking process, second is the temperature, which is the critical parameter to obtain a high fuel oil yield. The type of plastic also greatly affects the thermal cracking process. The type of reactor and its design are the key to any commercial process plant, as they determine the downstream product quality and the cost of separation.

The present study aims at production and optimization of value-added products from the thermal cracking of HDPE waste plastics. HDPE waste plastic is considered in the two forms one is covers and the other one is in the form of pellets for producing the value-added products. The effect of different process variable temperature, heating rate, residence time are used to explore the effect of process variables on the yield. The

produced value-added products can be used as feed stocks for chemicals and can be alternative solution to the land filling and reduces the green houses gases emissions. Design of experimental analysis technique is used to study the effect of independent variables on the yield of valuable products during the thermal cracking of HDPE waste plastic. The design of experimental study allows developing empirical model that can describe the dependence of key variables and their interaction. Several researchers have been investigated the conversion of plastics into value added products as listed in Table 1, based on the results it has been observed that these operating parameters play an important role in conversion of high-density plastics into value added products. Table 1 provides the over view of the different process variables considered for the for the production of value added products for the HDPE plastics, among the various independent variables considered temperature, heating rate and batch time plays an important role in production of value-added products and hence the effect of these independent variable on the response variables such as fuel oil, gases and solids are considered for the design of experimental approach.

The Response Surface Methodology (RSM) for pyrolysis of HDEPE using catalyst to produce liquid fuel has been studied by Kumar and Singh [46] to optimize process parameters. The RSM and FDM techniques is used to study the influence of experimental conditions on product yields from waste mixtures by pyrolysis has been used for optimizing the temperature, the initial pressure and reaction-time, to maximize the yield and composition of fuel oil products from the waste mixture studied [47], [48].

The novelty of the paper is the usage of a simple reactor setup along with the deployment of bentonite catalyst to transform HDPE plastics covers into useful products such as fuel oil, wax, grease and charcoal without leaving any residue. Moreover, the characteristics of resulting fuel oil is very similar to the commercial fuels.

Section snippets

HDPE waste plastic

Plastic products have been used in day-to-day activities especially for packaging many goods are often discarded after a single use which results in an inexhaustible generation of waste plastic materials. The waste plastic materials mainly consist of high-density

polyethylene. Especially in India every day to carry the things, goods, vegetables, and many food items the grocery bags are widely used. The waste plastics are collected from the household at local area in the Hyderabad city which …

Results and discussion

In the current study thermal degradation of waste plastics into value added products are studied at desired conditions. For the thermal cracking process the feed samples considered are described in Table 2, which consist of F1, F2, F3 and F4 with varying quantities of HDPE plastics and catalyst. The reaction is carried out using a reactor as shown in Fig. 1. The value-added products obtained after the thermal cracking process for the different feed samples F1, F2, F3 and F4 are shown in Fig. 2. …

Conclusions

The conversion of HDPE plastic waste covers into value added products by thermal cracking using bentonite is explored. The products obtained for designed feed samples during the thermal cracking are fuel oil, wax, grease and charcoal. Among the various produced products fuel oil occupies the major share and rest are in smaller portions. The density, viscosity, melting point, smoke point of fuel oil have been analyzed and compared with the conventional fuels. Based on the characteristics of the …

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CRediT authorship contribution statement

Ganesh Botla: Conceptualization, Visualization, Methodology, Investigation, Writing – original draft. **Praveen Barmavatu:** Investigation, Methodology, Writing – original draft. **Michael Pohorely:** Methodology, Validation, Writing – review & editing. **Michal Jeremias:** Funding acquisition, Methodology, Validation, Writing – review & editing. **Vineet Singh Sikarwar:** Conceptualization, Funding acquisition, Methodology, Supervision, Validation, Visualization, Writing – review & editing. …

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. …

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> …Meanwhile, the predictive capability of the model is assessed by plotting the predicted values against the actual molecular weights (Fig. S1). The close consistency between the predicted and actual molecular weights further confirms the superiority of the variance analysis results for this

> study [22,23]. Additionally, in this response surface model, the linear terms A, B, C and D, along with the quadratic terms A2, B2, C2 and D2, significantly affect the molecular weight of the copolymer, while the remaining terms are not significant.…

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Time-varying neural networks for multi-input multi-output systems: a reactive batch distillation modeling case study

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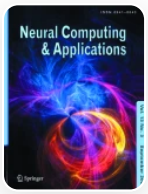

P. Naveen Kumar, B. Ganesh, M. Vamsi Teja & K. Yamuna Rani

Abstract

A novel time-varying neural network (TVNN) architecture incorporating time dependency explicitly, proposed recently, for modeling nonlinear non-stationary dynamic systems is further developed in the present study to extend it to multi-input multi-output (MIMO) systems, and two configurations are proposed to represent dynamics of multivariable batch chemical processes. The first model (TVNN-multi-input single-output (MISO) model) consists of an input layer with M inputs representing the past samples of process inputs and outputs, a hidden layer with polynomial activation function, and a second hidden layer of L neurons acted upon by an explicitly time-dependent modulation function, which are combined to result in the output layer with a

single output. This model is developed for each output in the MIMO system. In the second model (TVNN-MIMO model), multiple outputs are incorporated in the output layer. Back-propagation learning algorithm is formulated for the proposed neural network structures to determine the weights for each network configuration. The modeling capability of these networks is evaluated by employing it to represent the dynamics of a reactive batch distillation column for an esterification reaction. The results show that both the proposed neural networks configurations represent each composition of the reactive batch distillation dynamics accurately. Further, both the TVNNs exhibited better performance than time-independent networks trained using the same configuration. Both the TVNN configurations resulted in comparable performance, while the TVNN-MIMO model is more compact and requires less number of parameters. The present study illustrates that the proposed approach can be applied to represent dynamics of any batch/semi-batch process.

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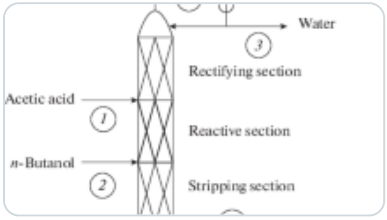

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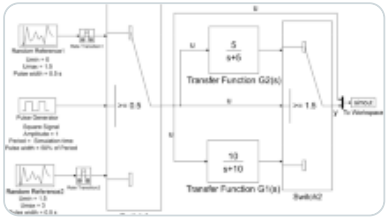

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The data used for model development have been generated through simulations and can be shared on specific request.

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Ethics declarations

Conflict of Interest

The authors declare that they have no conflicts of interest to disclose.

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Time-dependent modulation function

Reactive batch distillation column

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Original Article

Development of Nanosponge Formulations of Rosuvastatin for Oral Delivery Using a Central Composite Design

Sadhana Noothi[1,2], Narender Malothu[1,*], Vishnu Pulavarthy[2], Praveen BVS[3]

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ABSTRACT

Background: Rosuvastatin (ROS) is an anti-hyperlipidaemic drug which reduces cholesterol levels, having poor solubility and low bioavailability (<20%). The objective of the present study was to increase ROS bioavailability by formulating nanosponges. **Materials and Methods:** Important quality features were identified using the Quality by Design (QbD) method. Central Composite Design (CCD) was utilized to design formulations. Eudragit L-100 (EL-100) and Polyvinyl Alcohol (PVA) were used as polymers and surfactants, respectively. Nanosponges were produced using emulsion solvent evaporation (RF1-RF15). The final formulations were assessed based on parameters including drug-excipient interaction, particle size, surface morphology, Entrapment Efficiency (%EE), and *in vitro* drug release. The Design Expert-13 (DOE) produced the optimized Formulation (RF16), which was utilized in the *in vivo* drug release **Results:** All Formulations (RF1-RF15) showed particle size of 99±0.84 nm to 305±0.26 nm, %EE 17.8±0.42 to 84.69±0.45, and drug release was 94.33±0.45% to 99.77±0.56% in 4 hr. Optimized Formulation (RF16) showed a particle size of 295±0.35 nm, % EE of 78.54±0.26 %, and drug release study of 95.13±0.63% in 3.5 hr. The *in vivo* studies showed C_{max}, T_{max}, AUC_{0-t}, $AUC_{0-\alpha}$, $MRT_{0-\alpha}$ of the pure drug and RF16 of 7.123µg/mL and 14.787 µg/mL, 1.5 and 2.5 hr, 19.56 µg/mL*hr and 25.71 µg/mL*hr, 23.91 µg/ml*h, and 48.85 µg/mL*hr, 5.04 hr and 3.91 hr, respectively. **Conclusion:** The pharmacokinetic parameters RF16 demonstrate a 2-fold enhancement in the bioavailability of ROS nanosponges compared to the pure drug.

Keywords: Rosuvastatin, *In vivo* drug release, Central Composite Design, Eudragit L-100, Quality by Design.

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INTRODUCTION

Nanotechnology is one of the widely used technologies in the present times in physical and biological sciences.[1] Numerous uses of nanotechnology have been explored in nanomedicine and the development of nano-based drug delivery systems.[2] Within biomedicine, nanotechnology has been utilized in drug delivery, biosensors, nanobiotechnology, and tissue engineering.[3,4] Liposomes and micelles are examples of first-generation nanoparticle-based systems employed in these applications, followed by new-generation formulations like nanoparticles, nano-lipid carriers, and nanosponges used to deliver various drugs.[5] Targeting drug delivery mechanisms has long been a goal to get the desired result to avoid the vital issue of burst release in conventional delivery. Initially, the Nanosponge drug delivery system was only available as a topical administration method; however, in the twenty-first century, Nanosponges can be employed orally and Intravenously (IV). The nanosponge delivery method allows for regulated drug release. As a result, nanosponge delivery technology has gained popularity to improve therapeutic efficacy at the target site.[6]

ROS is an HMG-CoA reductase inhibitor and anti-hyperlipidaemic drug that reduces cholesterol synthesis through HMG-CoA conversion to mevalonic acid.[7,8] However, it has poor solubility and less than 20% bioavailability. Different formulations, such as solid dispersions and solid lipid nanoparticles, have been explored to improve ROS bioavailability; these preparations are complicated and may present multiple stability concerns.[9]

Pharmaceutical development using the Quality by Design (QbD) methodology emphasizes on recognizing and managing process and product variability within established limits to provide high-quality products.[10] QbD was utilized in the formulation of ROS nanosponges to determine the Quality Target Product Profile (QTPP), identify Critical Quality Attributes (CQA), specify essential process parameters, and assess and control risk using Failure Mode and Effects Analysis (FEMA).[11] Following

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the identification of CQAs, the ROS nanosponge Formulations (RF) were designed using a central composite design approach within response surface methodology (RSM), and an optimized formulation was selected based on how independent factors (X) affect the responses (CQAs) (Y) and subsequently evaluated for *in vivo* release profile.[12,13] The current study aims to design and develop drug-loaded nanosponges to increase the drug's solubility and bioavailability. Different ratios of surfactant and polymer were used to generate nanosponges and further evaluated pharmacokinetic parameters.

MATERIALS AND METHODS

Materials

The API was acquired as a gift sample from Hetero Drugs, Hyderabad. Eudragit L-100 was procured as a gift sample from Lee Pharma Limited., Visakhapatnam, India. Solvents, Poly Vinyl Alcohol, and other chemicals (AR grade) were procured from SDFCL, Mumbai.

Methods

Determination of CQA and QTPP

CQAs are the biological, chemical, physical, or microbiological characteristics or features that should be controlled within specific parameters to ensure the desired quality of a pharmaceutical formulation. CQAs are identified based on scientific knowledge, experience, and regulatory guidelines. These attributes directly or indirectly affect the efficiency and safety of the drug.[14] The QTPP represents a drug product's desired characteristics and attributes that will ensure its safety, efficiency, and overall quality. It is a comprehensive summary of the quality criteria a drug formulation should meet to be considered for its intended application.

Screening factors and risk assessment

Screening factors involve the systematic evaluation of different factors or variables that could impact the quality or performance of a product or process. These factors include process parameters, raw materials, formulation components, equipment, and environmental conditions. Screening factors aim to identify the parameters which significantly impact the desired outcomes or pose risks to product quality. Risk assessment is a systematic approach to identifying, evaluating, and prioritizing potential risks associated with a product, process, or activity. Various materials and process parameters attributes were developed using the Ishikawa fishbone illustration,[15] which may cause a variance of CQAs to lead to product failure. From the literature review, material attributes like the concentration of the polymer and copolymer and process parameters like stirring speed were considered screening factors; particle size, %EE, and *in vitro* drug release are considered CQAs for QTPP.

Experimental design

After identifying the Critical Quality Attributes (CQAs) and variables, the formulation must be optimized and refined. Nevertheless, it is critical to conduct multiple tests, and addressing interaction studies that incorporate variables can be pretty complicated. Design Expert-13.[16] software's Central Composite Design (CCD) function was utilized to create the nanosponge formulations for this study. It improves the formulation and identifies the interaction effects of the factors on the responses in an efficient manner. Dosages of ROS drug release (Y_3), EL100 (X_1), PVA (X_2), and swirling speed (X_3) were taken into account during the design of the nanosponge. Y represents the response, while X denotes the independent variable. Considering the levels -1 and +1 for both independent variables, every conceivable formulation combination was generated.[17]

Optimization of the model

After the first study, a rotatable CCD in Response Surface Methodology (RSM) was utilized for the optimization of the dependent variables: drug release (Y_3), %EE (Y_2), and particle size (Y_1). Three repetitions of the examinations were performed in a random order. Checkpoint formulations were prepared to validate the design space. The experimental results were fitted to polynomial models that included interactive terms, as per the following equation:

$$Y=\beta_0+\beta_1X_1+\beta_2X_2+\beta_3X_3+\beta_{12}X_{12}+\beta_{22}X_{22}+\beta_1\beta_2X_1X_2 \quad [1]$$

The statistical significance ($p<0.05$) of the model coefficient was analyzed by performing an Analysis of Variance (ANOVA).

Preparation of ROS nanosponges (RF)

ROS nanosponges (RF1-RF15) were prepared using the emulsion solvent evaporation technique. EL100 was employed as a polymer, and PVA was used as a surfactant. CCD specified the choice of polymer and surfactant concentrations.[18] First, the organic phase was produced by dissolving appropriate amounts of EL100 and ROS in dichloromethane. PVA was dissolved in distilled water (100 mL) to prepare the aqueous phase. The two phases were combined by adding an organic phase dropwise into the continuous aqueous phase and stirring for 2 hr at 1000 rpm. The formed nanosponges were vacuum-filtered and dried at 40°C for 24 hr before being stored in a desiccator.[19]

Compatibility study of drug-excipient

The spectra of the ROS and RF samples were determined using FTIR (Shimadzu FTIR-8400S) within the 400-4000 cm^{-1} range. The KBr pellet method is used. The pellet-forming process was achieved by combining a minute quantity of the substance with potassium bromide under pressure.[20,21]

SEM Analysis

The ROS was morphologically characterized using scanning electron microscope (Carl Zeiss SEM with Oxford EDX) in a high vacuum mode.[22]

Particle size, Zeta potential, and Polydispersity Index (PDI)

Zetasizer (Malvern Nano ZS) was used to determine the average particle size, PDI, and surface charge of RF. distilled water was added to each sample for dilution before analysis and analysed at 250.5°C.[23]

XRD study

The XRD (XRD-7000/Shimadzu) was used to study the formulation of ROS nanosponges by exposing the API to Cu Kα radiation.[24]

DSC study

In order to identify the interaction between the drug and excipient during formulation, Differential Scanning Calorimetry (Shimadzu DSC-60) tests were performed on the ROS nanosponge formulation and API.[25]

% EE and drug loading capacity (%DL)

The percentage of drug entrapped inside the nanosponge formulation is referred to as %EE.[26] To determine the %DL and % EE, 50 mg of RF was dissolved in 10 mL of phosphate buffer (pH 6.8), and the sample was agitated until complete dissolution. The resulting transparent drug layer was collected for analysis. The amount of ROS in the nanosponges was evaluated utilizing a UV-visible spectrophotometer, and the % EE of the ROS was calculated.[27]

$$\%EE = \frac{Total\ amout\ drug - Free\ drug\ in\ solution}{Total\ amount\ of\ drug} \times 100$$

$$\%DL = \frac{Total\ amount\ of\ drug - Free\ drug\ in\ solution}{Total\ wt\ of\ nanosponges} \times 100$$

In vitro drug release study

The dissolving apparatus USP-II (paddle method, Labtronics dissolution apparatus) was used to estimate the drug release within a temperature range of 37±0.2°C. Phosphate buffer of 900 mL at a pH 6.8 and100 rpm was used.[28] Nanosponges, equivalent to 20 mg of the drug, were measured, packed into a diffusion sachet, and placed into a dissolution beaker for drug dissolution testing. UV-vis spectral analysis at 237 nm evaluated the drug's concentration after samples were taken at specific intervals ranging from 1 to 8 hr.[29] The release pattern of RF's medication was examined by fitting the results of each dissolving sample into the most appropriate kinetic models.[30,31]

In vivo release study

When the plasma concentrations of the nanosponge formulation and the purified drug were compared, an *in vivo* drug release study revealed comparable outcomes. A PK solver 2.0.[32] was employed to determine the pharmacokinetic parameters. For an *in vivo* drug release experiment, healthy rabbits weighing between 1.5 and 2.5 kg were divided into the following three groups: standard (group I), test (group II), and control (group III). Animals are subjected to fasting for 24 hr before the drug administration.[33] Group I was administered the drug solution in its most purified form, while Group II was administered a nanosponge formulation containing 10 mg/kg of ROS. Group III included the control animals. At 1, 2, 3, 4, 6, 8, 10, and 12 hr, blood was taken from the rabbit's marginal ear vein. After undergoing micro centrifugation at 5000 rpm, the plasma was chilled to -20°C.

The plasma was separated from the blood sample by centrifuging for 5 min at 5000 rpm. A protein precipitant (0.2 mL of 20% perchloric acid) was combined with the collected plasma sample, and the drug was extracted from the plasma by centrifugation at 4000 rpm for 10 min at 4°C. Valsartan (an internal standard) was added to the plasma sample. The ROS and valsartan were injected into HPLC (Shimadzu SPD-20A LC-20AD) to measure the ROS in the extracted drug solution. Various concentrations of ROS solutions (0.4 -1.6 µg/mL) were prepared for calibration at 237 nm.[34] The column used for chromatography was the C18 (Cosmos) column. The mobile phase used for the separation is Acetonitrile: 5 mM sodium acetate buffer (70:30), the flow rate is 1mL/min, and the Injection volume is 5 µL.

Stability study

The samples were preserved in stability chambers characterized by a relative humidity of 75% and a temperature of 40±0.5°C. Physical examination and *in vitro* drug release assays were performed on the formulations over six months.

RESULTS

Determination of QTPP and CQAs for rosuvastatin nanosponges

The first phase of QbD for product development is determining the QTPP. The QTPP is a quality attribute set that ensures the efficacy and safety of the product. The QTPP outline is presented in Table 1. The Second phase of the QbD involves choosing the CQAs. The Critical Quality Attributes (CQAs) derived from the QTPP impact the finished product; hence, monitoring and researching this effect is essential.

Determination of CMAs, CPPs, and screening of factors

It was determined which CPPs and CMAs impacted the product quality. The concentrations of the polymer and stabilizer were thought to be the main CMAs determining the effectiveness

Table 1: QTPP of ROS nanosponges.

QTPP	Target	Justification
Formulation	Nanosponge	Particle nanonization is used to improve medication solubility while also achieving predictable drug release.
Particle size	<500 nm	Varying particle size affects the drug loading and release rate.
% EE	Maximum	Low %EE leads to loss of drugs in the system.
Percent yield	-	Process-related problems are indicated.
Drug release	Maximum	The particle's porosity impacts the drug release.

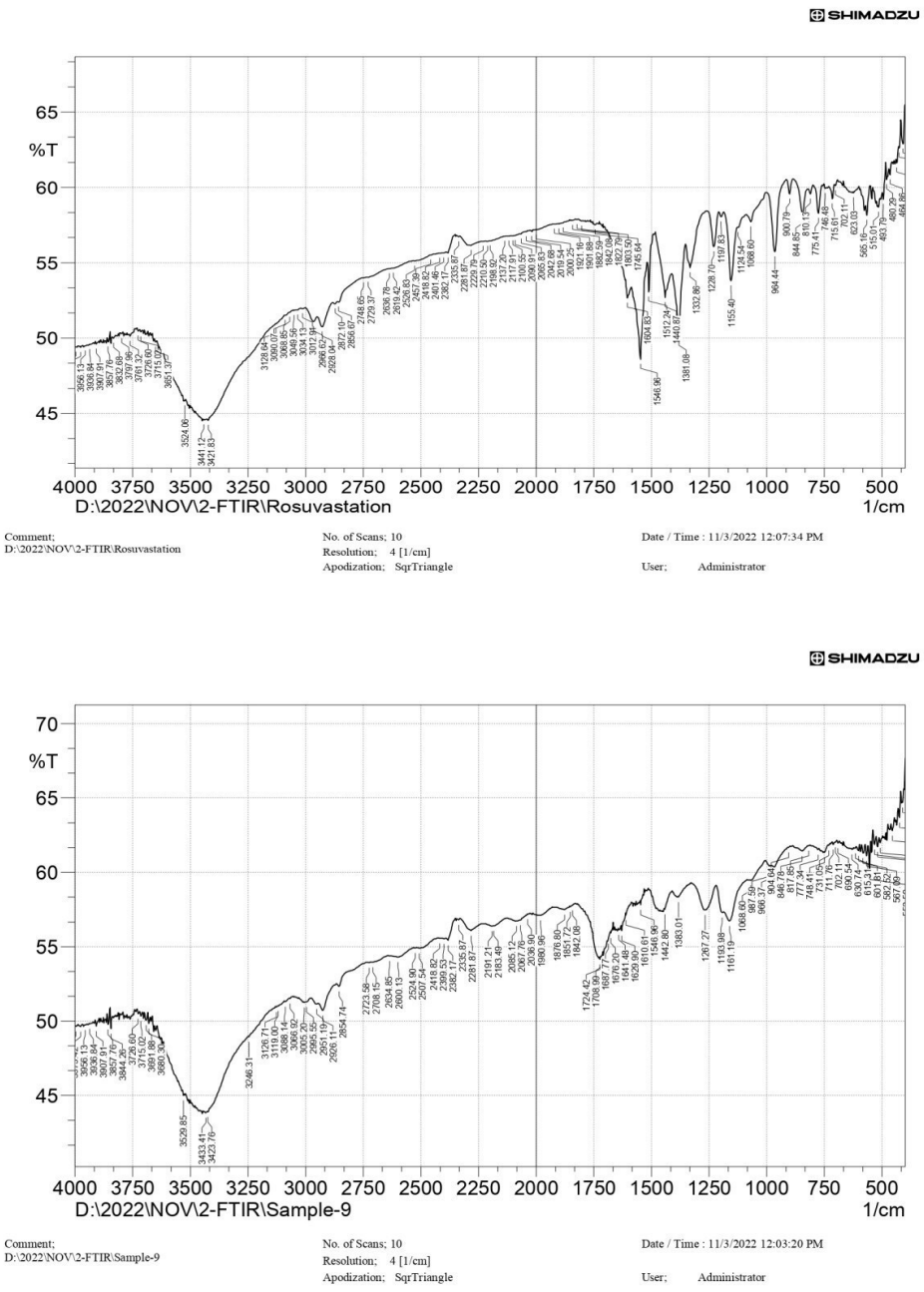


Figure 1: FTIR spectra of Pure drug (a) and ROS nanosponge (R16) (b).

of particle entrapment and particle size. The stirring rate and duration were identified as the process parameters that would have affected the nano formulation's particle size distribution and entrapment effectiveness. Various material variables and critical process parameters are represented in the Ishikawa illustration. From the literature review and preliminary studies, the polymer concentration (EL100), stabilizer concentration (PVA), and stirring speed (RPM) are considered critical factors in the present study.

Drug-excipient compatibility study

The FTIR spectrum of pure ROS and its nanosponge sample showed distinctive peaks for OH stretching at 3421 and 3433 cm^{-1}, C=O 1745 and 1842 cm^{-1}, C=C at 1604 and 1527cm^{-1}, C=N stretching at 1546 and 1629 cm^{-1}, C-F and S=O bending1332 and 1383 cm^{-1}, and so on. The two spectrums showed no interaction between pure drug and nanosponges, and the difference between the peaks of the pure drug and a nanosponge was less than 100 cm^{-1} (Figure 1).

SEM analysis

As per the SEM analysis, the nanosponge Formulation (RF1-RF15) achieved particle size ranging from 99.24±0.84 to 305.35±0.26 nm (Table 2). As shown in Figure 2a, the nanosponge surface had no trace of any crystalline medication particles, and the particle diameters of all formulations remained constant.

Particle size, PDI, Zeta Potential

The optimal formulation (RF16) contained particles that were nanosized and maintained in separation by repulsive forces, as shown in Figure 2b: the average particle size was 294±0.35 nm, the zeta potential was +16.1 mV, and the PDI was 0.489.

XRD study

The confirmation of the formation of ROS nanosponges was illustrated in Figure 2c by observing a smoother XRD curve for the ROS nanosponges relative to a purified substance.

DSC study

An endothermic peak for melting was observed at 138.07 °C on the DSC thermogram of the ROS pure substance. The inclusion of Rosuvastatin in the amorphous nanosponge core is indicated in Figure 2d, as the endothermic peak of the nanosponge was 254.81°C, which is in closer proximity to the 234.33°C peak of EL100.

%EE and %DL

The drug %EE and %DL capacity of all the nanosponges (RF1-RF15) were observed between 17.8±0.42 to 84.69±0.45% and 9.12±0.68 to 34.54±0.56%, respectively, and are shown in Table 2.

In vitro dissolution study

The ROS nanosponges (RF1-RF15) dissolution study was conducted using a USP-II dissolution apparatus at 37±0.5°C with 100 rpm using phosphate buffer (pH-6.8). Samples were collected at 0, 0.5, 1, 1.5, 2, 2.5, 3, 4 and 6 hr. Drug release rates for all formulations ranged from 94.33±0.45% to 99.77±0.56% within 4 hr (Figure 3). Findings from the study of release kinetics using the Higuchi diffusion mechanism showed that the formulations exhibited zero-order kinetics.

Experimental design-Fitting response surface curve

The ROS nanosponges were assessed regarding particle size change, drug release, and %EE. Statistical analysis was performed on the formulation data to ascertain the model that most accurately corresponds to the independent variables. Compiled were regression results (*p*-values), coded equations, and regression coefficients (R^2) about the dependent variables. The significance of the constructed linear polynomial models was assessed through Analysis of Variance (ANOVA) (Table 3). Three-dimensional plots were used to study how the two independent variables interacted with one another (Figure 4).

Effect of Independent Variables on Particle Size, %EE, and Drug Release

The ANOVA results indicated that the linear model was the most appropriate for response 1, which concerns particle size. X1 and X2 were shown to be significant factors with agonistic impacts on particle size, but X3 did not show statistical significance. %EE demonstrated the linear model as the most suitable model. The significant factors X1 and X2 had a notable impact on the %EE. The linear model identified X1, X2, and X3 as crucial components that interacted in opposition to each other in drug release.

Validation of the model

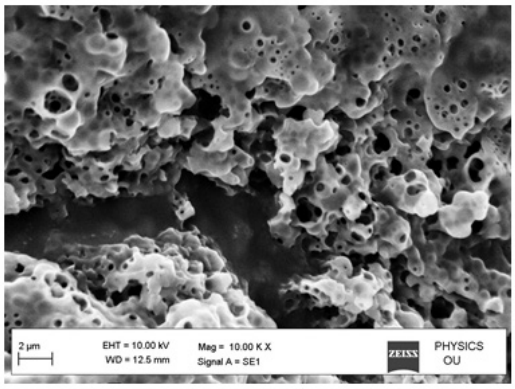
ROS nanosponges optimization aimed to increase the percentage of EE, decrease the particle size, and optimize drug release. Among the twenty-eight responses provided by the program, one produced a desirability of 0.462; this value served as the formula for batch RF16. In conclusion, the formulation in sample RF16 was deemed to be preferable.

Evaluation of Optimized formulation

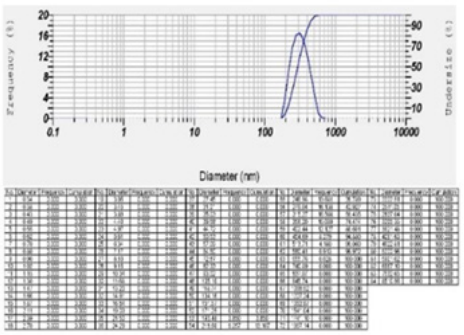
Table 4 exhibits RF16, the statistically optimized optimum formula, and provides an account of the parameter evaluation outcomes for the modified formula.

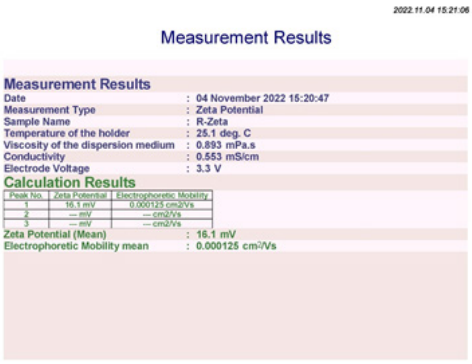
In vivo release study

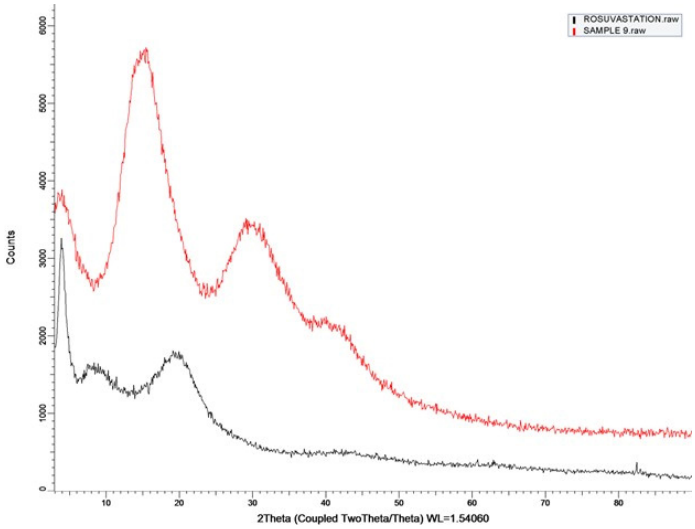
The investigation of drug release *in vivo* employed the optimized formulation RF16, characterized by exceptional particle size, an ideal percent efficacy, and drug release *in vitro*. Extracted drug samples were estimated for the concentration of the drug



(a) SEM Image for RF16







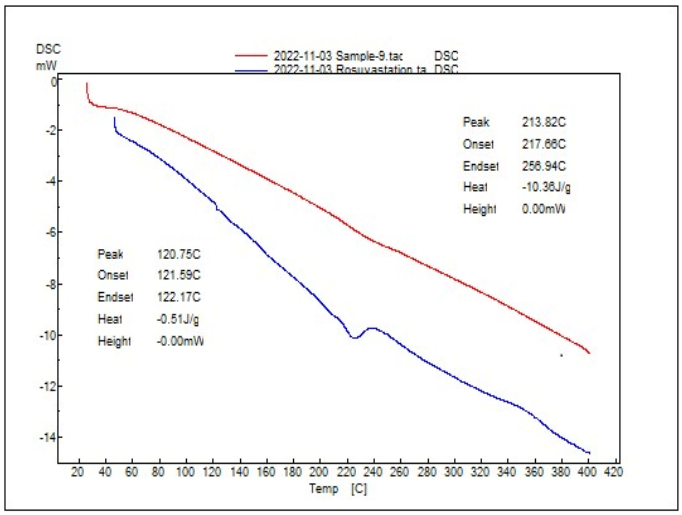


Figure 2: Characterization of nanosponges (a) FTIR (b)Particle size and zeta potential (c) XRD and(d) DSC.

using HPLC. C_{max}, T_{max}, and AUC the three pharmacokinetic parameters were evaluated and are are reported in Figure 5 which shows the levels of the medicine and ROS nanosponges (RF16) in the blood after they were taken orally. The results indicate that the C_{max} and T_{max} values for the purified substance and RF16 were 7.123 µg/mL, 14.787 µg/mL, and 1.5 and 2.5 hr, respectively. The $MRT_{0-\alpha}$ value for pure drug and RF16 were 5.04 hr and 3.91 hr, respectively. The $AUC_{0-\alpha}$ values for RF16 were 48.85 µg/mL*hr, while the $MRT_{0-\alpha}$ values were 19.56 µg/mL*hr and 25.71 µg/mL*hr for pure drug. The AUC results demonstrated that the drug was much more bioavailable in the nanosponges compared to the pure drug. Additionally, distinct pharmacokinetic characteristics were observed between the two groups.

Table 2: Drug loading (%) capacity for all formulations.

Formulation	Particle size (nm)	% EE	% DL
RF1	206	33.66±0.45	20.45±0.35
RF2	156	26.66±0.34	15.49±0.54
RF3	99	17.8±0.42	9.12±0.68
RF4	192	46.14±0.23	25.35±0.32
RF5	206	44.16±0.35	23.65±0.43
RF6	187	42.3±0.56	22.24±0.45
RF7	136	20.3±0.46	12.65±0.56
RF8	103	19.4±0.67	11.68±0.25
RF9	197	39.5±0.56	21.46±0.52
RF10	205	32.7±0.43	19.56±0.26
RF11	295	64.46±0.35	32.45±0.43
RF12	305	84.69±0.45	34.54±0.56
RF13	289	73.76±0.38	22.67±0.65
RF14	258	46.4±0.46	25.56±0.54
RF15	197	34.48±0.54	20.56±0.48

Table 3: Equations, probability, regression values, and the final models.

Sl. No.	Dependent Variable	Coded Equation	R^2 Value	*p*-value	F-value
1	Particle Size	202.07+43.80(A)+45.75(B)+2.21(C)	0.957	<0.0001	83.19
2	%EE	41.76+11.80(A)+13.83(B)+1.25(C)	0.84	<0.0001	19.24
3	%Drug release	95.77-2.56(A)-3.53(B)-0.2953(C)-2.83(AB)-0.355(AC)-0.82(BC)	0.9281	0.0004	17.20

Table 4: Formulation and evaluation of optimized formulation.

Ingredients	RF16	Responses	Predicted	Observed
Eudragit L100 (mg)	361.33	Particle size	252.75 nm	295±0.35 nm
PVA (mg)	472.14	%EE	58.52%	78.54±0.26%
RPM	1500	Drug release (at 4 hr)	90.08%	96.13±0.63%

DISCUSSION

A wide range of nanosponge formulations (RF1-RF15) were experimentally designed utilizing the Design Expert-13 software. The assessment of external variables' effects on CCD is achieved by implementing the surface response approach. The surface response method showed that polymer (EL100) has more influence on the size and %EE of the ROS nanosponges when compared with surfactant (PVA). The nanosponge formulation achieved particle size ranging from 99.24±0.84 to 305.35±0.26 nm for all the Formulations (RF1-RF15), and the optimized Formulation (RF16) showed 294±0.35 nm, the PDI was 0.489, and the zeta potential was 16.1 mV, indicating that the nanosized particles and separated by repulsive forces.

Predictions generated throughout the design process facilitated the identification of the compatibility between the excipient and the medication. Based on the characterization data, including FTIR spectra, it was observed that the API and formulation exhibited distinct absorption peaks. Furthermore, the absorbance shifts remained within the acceptable range of 100 cm^{-1} absorbance variations, effectively ruling out any potential incompatibility between the excipients and the medication. The XRD patterns of purified drug and ROS nanosponges were notably dissimilar. The gentler trajectory of the former indicated that the drug was encapsulated in an amorphous nanosponge complex. In contrast, the distinct peaks of the latter suggested that the drug existed in crystalline form. An endothermic apex for melting was observed at 138.07°C on the DSC thermogram of the pure substance of the ROS. Because the endothermic peak of EL100 occurred at 234.33°C and the endothermic peak of nanosponges occurred at 254.81°C, it was determined that the amorphous nanosponge core comprised Rosuvastatin.

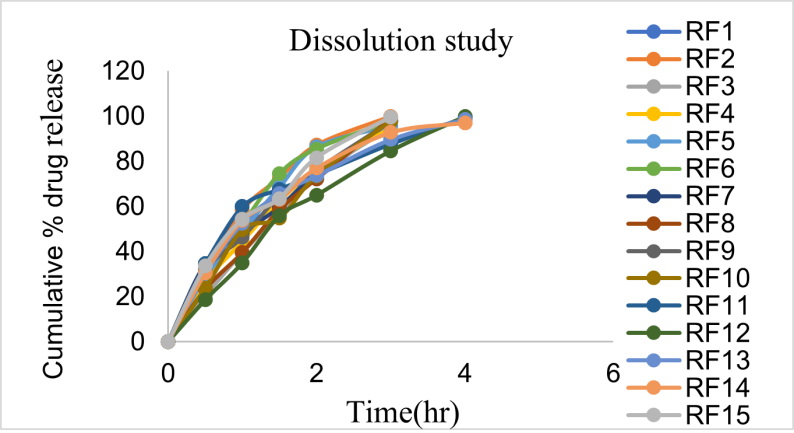


Figure 3: *In vitro* drug release profile for ROS formulations (RF1-RF15).

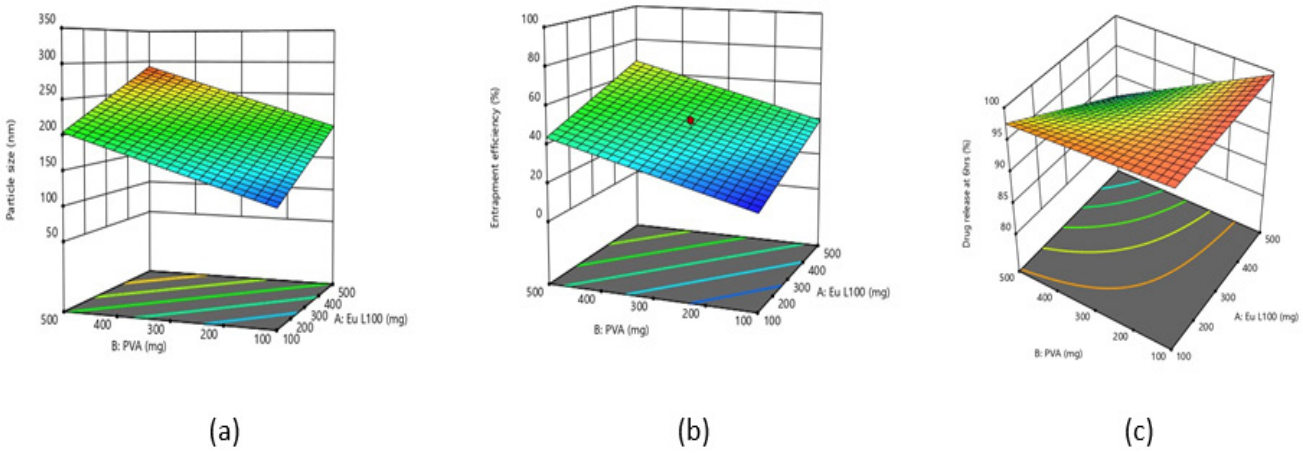


Figure 4: Surface response plots showing an effect between Eudragit L100 and PVA on particle size (a), % EE (b), and Drug release at 4 hr (c).

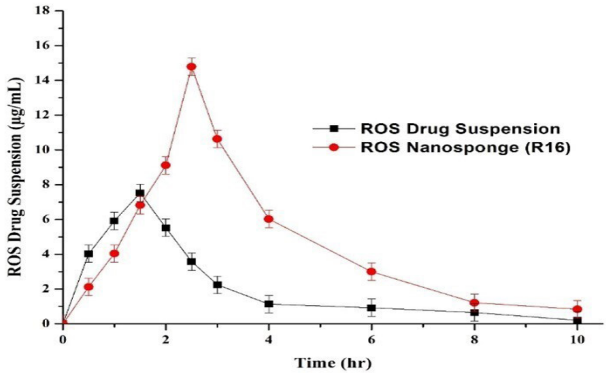


Figure 5: *In vivo* study of pure drug and ROS nanosponges (RF16).

The drug %EE of all the nanosponges (RF1-RF15) was observed between 17.8±0.42 to 84.69±0.45%, and the optimized formulation showed %EE 78.54±0.26. *In vitro* drug release study of optimized formulation results indicate that ROS enclosed in the nanosponge (RF16) absorbs better than pure drug. The time to maximum concentration (C_{max}) for the pure drug was 1.5 hr and for RF16 it was 2.5 hr, according to the *in vivo* release kinetics. The C_{max} values for the two substances were 7.123 µg/mL and 14.787 µg/mL, respectively. The AUC_{0-t} for the pure drug was 19.56 µg/mL*hr, while for RF16 it was 25.71 µg/mL*hr. The $AUC_{0-\alpha}$ for the pure drug was 23.91 µg/ml*h, while for RF16 it was 48.85 µg/mL*hr. The $MRT_{0-\alpha}$ for the pure drug was 5.04 hr and

for RF16 it was 3.91 hr. The *in vivo* pharmacokinetic properties of the purified drug and RF16 were dissimilar, indicating that RF16 exhibited a twofold drug release enhancement compared to the pure drug. The area under the curve data also demonstrated that the medication's bioavailability was much improved in nanosponges compared to the pure drug.

CONCLUSION

An experimental approach was used to design different nanosponge formulations using Design Expert-13. The surface response curves showed that polymer A (EL100) affects the size and EE (%) of ROS nanosponges more than surfactant (PVA). All the formulated ROS nanosponges exhibited high EE (%), drug loading capacity, and % drug release. The optimized formulation (RF16) was used in *in vivo* experiments. *In vivo* studies indicated that the optimized formulation (RF16) showed a 2-fold increase in drug bioavailability than the pure drug. As a result, the current investigation led to the conclusion that the nanosponge formulation exhibited potential and could be utilized to develop ROS delivery systems that are more accessible and efficient.

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AUTHOR CONTRIBUTIONS

All authors contributed to the conception and design of the study. Sadhana N, BVS Praveen, and Vishnu P performed material preparation, data collection, and analysis. Sadhana N and Narender M wrote the manuscript's first draft, and all authors commented on earlier versions. All authors read and approved the final manuscript.

ETHICAL APPROVAL

All animal studies were conducted with prior approval from the Institutional Animal Ethical Committee (approval no. 06/IAEC/VIPER/Ph.D/2021-22/II).

ANIMAL STUDIES

All institutional and national guidelines for the care and use of laboratory animals were followed.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

FTIR: Fourier-transform infrared spectroscopy; **DSC:** Differential Scanning Calorimetry; **XRD:** X-ray Diffraction; **SEM:** Scanning Electron Microscopy.

SUMMARY

In the present work, the Rosuvastatin (ROS) nanosponges were formulated using the emulsion solvent evaporation method by employing the QbD approach and CCD in response surface methodology in the Design of Experiments (DoE). When assessing the synthesized nanosponges, several factors were considered, including particle size, Entrapment Efficiency (%EE) percentage, *in vitro* drug release research, and *in vivo* drug release. The produced nanosponges exhibited a particle size range of 99±0.84 to 305±0.26. The percentage of Effective Release (%EE) varied between 17.8±0.42 and 84.69±0.45. The substance showed a 4 hr release range of 94.33±0.45 to 99.77±0.56. The drug release study yielded results for the enhanced Formulation (RF16) in 3.5 hr: a rate of 95.13±0.63%, a particle size of 295±0.35 nm, and an efficiency evaluation of 78.54±0.26%. *In vivo* study indicated the 7.123 µg/mL and 14.787 µg/mL, 1.5 and 2.5 hr, 19.56 µg/mL*hr and 25.71 µg/mL*hr, 23.91 µg/ml*h and 48.85 µg/mL*hr, 5.04 hr and 3.91 hr of C_{max}, T_{max}, AUC_{0-t}, $AUC_{0-\alpha}$, $MRT_{0-\alpha}$ for the pure drug and RF16, respectively. The present study confirmed that the nanosponge formulation was the most suitable approach to enhance the solubility of ROS.

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Pencil Graphite Electrodes Enhanced with Green Synthesized Nano Particles as Efficient Electrocatalysts for Application in Bio-Fuel Cells

Original Article Published: 02 July 2024

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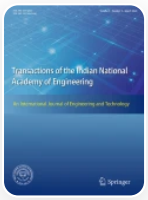

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Aims and scope

Submit manuscript

D. Shruthi Keerthi, M. Mukunda Vani & Balaji Krishnamurthy

Abstract

Over the past decade, the integration of nanomaterials into electrode surfaces has gained significant attention due to their unique properties and enhanced performance in various applications. Copper and silver nanoparticles prepared through green synthesis using plant extracts have shown great potential in enzymatic biofuel cells when coated with pencil graphite electrodes (PGEs). This work investigates the performance of cost-effective, green-synthesized copper and silver nanomaterials (from *Rosa centifolia*) when integrated with pencil graphite electrodes. A suitable grade pencil lead is coated with the obtained copper and silver nanoparticles to obtain modified electrodes. Electrochemical and morphological characterizations are carried out using cyclic voltammetry (CV),

Electrochemical impedance spectroscopy (EIS), open circuit potential (OCP), scanning electron microscope (SEM), X-ray diffraction spectrophotometry (XRD), and nuclear magnetic resonance spectroscopy (NMR). In a half-cell electrode assembly, AgNP/ PGE (silver nanoparticles coated electrode) anode with 2B grade resulted in a higher current density of 2450 $\mu A\ cm^{-2}$, followed by a CuNP/ PGE (copper nanoparticles coated electrode) anode with 2B grade with a current density of 1090 $\mu A\ cm^{-2}$ when compared to bare PGE with 2B grade with a current density 764 $\mu A\ cm^{-2}$. EIS measurements showed lower R_{ct} values for AgNP/PGE (0.7 mm) 2B (930 Ω) and CuNP/PGE (0.7 mm) 2B (1529.1 Ω) compared to bare/PGE (0.7 mm) 2B (3755.7 Ω). The EIS data indicates improved electron transfer through the redox couple due to Ag and Cu nanoparticles on the electrode surface. Therefore, 2B grade AgNP/PGE exhibits better electron transfer kinetics with improved surface area, resulting in high-performing electrodes, providing scope for future renewable energy production.

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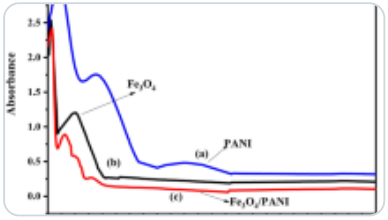

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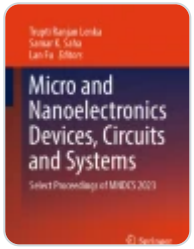

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Data availability

Data will be provided on request.

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Ethics declarations

Conflict of Interest

All authors postulate that they have no conflict of interest to disclose.

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RESEARCH Open Access

Optimizing organically nano-fabricated Ni metal complexes for enhanced antioxidant and anticancer activity using response surface methodology

Swathi Aleti[1*], Savita Belwal[1] and Mukunda Vani Medala[2]

Abstract

Background Researchers, prompted by the toxicity and side effects associated with cisplatin, are exploring alternative approaches for developing transition metal-based anticancer agents. Employing a green biochemical approach, we transformed Nickel pyridine dicarboxylic acid compounds into the nanoscale using the aqueous extract of Macrotyloma uniflorum (horse gram).

Results Characterization of the biosynthesized nanoparticles involved electronic and IR spectroscopy. A scanning electron microscope revealed a predominant spherical shape for most Nickel nanoparticles (Ni-NPs), with XRD patterns indicating particle sizes ranging from approximately 30–150 nm. The nanoparticles were evaluated for their free radical scavenging efficiency and in vitro anti-malignant properties against HeLa and A549 cancer cell lines. Numerical optimization of the DPPH and MTT assays was conducted using response surface methodology (RSM), focusing on the effects of 3,4-pyridine dicarboxylic acid (ML_1), 2,4-pyridine dicarboxylic acid (ML_2), nickel nanoparticles concentration, and temperature. In this investigation, the incorporation of Horse Gram seed extract (Macrotyloma uniflorum) has unveiled its abundance in phenolic and flavonoid compounds, widely acknowledged for their robust antioxidant activity in the existing literature.

Conclusion The present study highlights the potential for refining the bio-toxicity and biochemical attributes of Ni-NPs to pave the way for a new generation of versatile anticancer agents with clinically established efficacy. Notably, the anticipated data closely corresponds with experimental outcomes, reinforcing the trustworthiness and validity of the RSM model for examining anticancer and antioxidant properties in this context. ML_2 exhibited heightened antioxidant and anticancer activities in comparison to ML_1 nanoparticles.

Keywords Biosynthesized Ni-NPs, *Macrotyloma uniflorum*, SEM, XRD, Antioxidant, Anti-cancer activity, Response surface methodology

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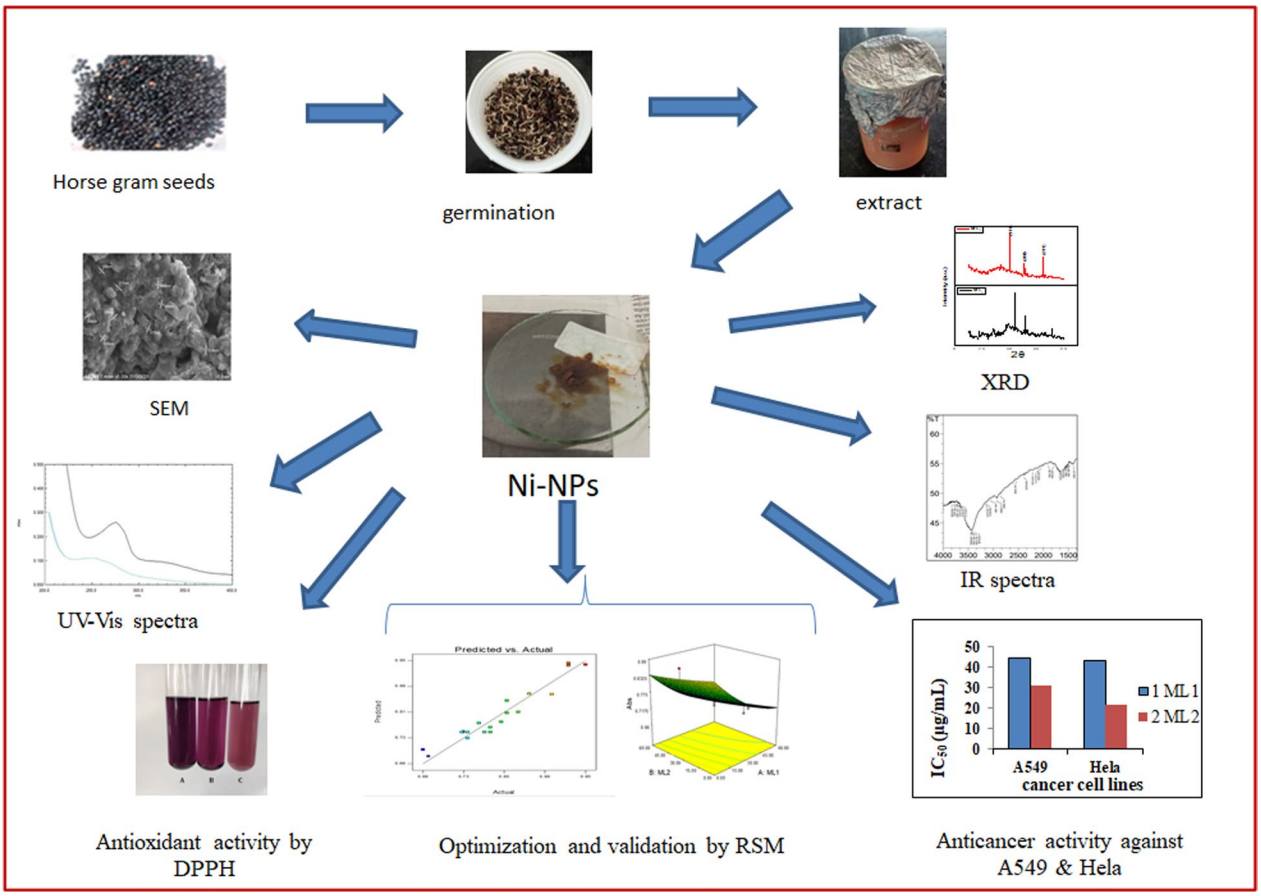
Graphical abstract



Background

Nanoparticles derived from metals exhibit a range of advantageous properties, including excellent conductivity, a significant surface-to-volume ratio, and notable nano-plasmonic characteristics [1]. The extensive study of metal nanoparticles is driven by their potential applications in sensor devices, bio-devices, data storage, catalytic processes, and spectrophotometric techniques [2]. Biogenic nano-sized particles obtained from plant-based materials offer a straightforward and time-efficient synthesis method, with plant extracts proving more conducive to size reduction compared to microbiological cultures [3]. Literature supports the efficacy of botanical extracts in treating skin diseases, outperforming results obtained from various microbes [4].

In this research, the focus is on exploring different ligands for the creation of Ni-nanoparticles. Two isomers of pyridine dicarboxylic acid, namely pyridine-2, 4-dicarboxylic acid (Lutidinic acid) and pyridine-3,4-dicarboxylic acid (Cinchomeronic acid), have been selected as ligands for the study in conjunction with Nickel metal. Lutidinic Acid, recognized as a corrosion inhibitor [5], is also noted for its cytotoxic nature [6]. The objective is to examine the outcomes of these ligands in the synthesis of Ni nanoparticles.

The rationale behind selecting the organic moiety pyridine-2, 4-dicarboxylic acid and its derivatives for the study is clear. These compounds have demonstrated significant effects on physiological activity, acting as immuno-suppressants [7] and fibrous-repressive drugs crucial for the initiation and growth of certain plant

families [8]. Additionally, they play a protective role by preserving specific enzymes in the cells of Bacillus subtilis species under temperature reduction conditions [9]. Notably, the pyridine compound with 2,4-dicarboxylic acid features structure identical to 2-oxoglutarate, a well-known inhibitor of 2-oxoglutarate-dependent dioxygenases. This inhibition, as observed in the growth of tomato seedlings exposed to various concentrations of pyridine dicarboxylic acid, resulted in diminished root size and smaller epicotyl [10].

Bio-nanotechnology involves the synthesis of nanoparticles through the utilization of organic biomolecules, encompassing living organisms such as fungi, bacteria, herb, yeast, as well as various naturally occurring moieties like proteins, peptides, sugar and vitamins [11, 12].

The integration of physical and chemical methodologies with fundamental standards, such as redox reactions, in the presence of biological adjuvants or natural phytonutrients, results in the production of nanoparticles with specific functions [13]. The biological synthesis of nanoparticles offers an environmentally friendly, uncomplicated, and cost-effective approach for researchers. This method also possesses the advantage of stabilizing nanoparticles through the utilization of plant secondary metabolites, serve equally reducing and capping molecules. Notably, nanoparticles produced using green technology exhibit minimal toxicity compared to chemically prepared counterparts, making them efficient carriers for drug delivery systems in in vivo applications [14].

Nickel nanoparticles, for instance, show promising applications in various fields including magnetism [15], microelectronics, power skills [16], and biomedical applications [17]. Due to their rapid reactivity, ease of operation, and environmentally friendly properties, nanoparticles play a pivotal role in accelerating various organic reactions. These include oxidative coupling of thiols with multiple reaction pathways [18], reduction of aldehydes and ketones [19], hydrogenation of olefins [20], preparation of stilbenes through alcohol by Wittig-olefination [21], and α-alkylation of ketones [22]. Furthermore, they serve as catalysts for the decomposition of ammonia and its products [23]. A cutting-edge application of nanoparticles involves the fabrication of nanotubes, particularly carbon nanotubes (CNTs) [24].

The literature extensively covers the biological synthesis, characteristics, and applications of both Ni and Ni-oxide nanoparticles, with numerous articles and reviews focusing on environmentally friendly approaches for their preparation [25]. Nasseri et al. presented a method for synthesizing NiO nanoparticles using an aqueous extract of Tamarix serotina, showcasing their catalytic properties and confirming the nanoparticles' size to be in the range of 10–15 nm with a cuboid shape [26].

Presently, various plants segments, including leaves, flowers, seeds, fruits, barks, and peels, are employed for distillation to produce nanoparticles [27]. The plant distillate, rich in phytonutrients, antioxidants, and essential organic compounds, holds potential therapeutic significance [28, 29]. Over the past decade, the preparation and fabrication of nickel oxide nanoparticles have been continuously advancing, exploring their applications in various natural biological systems [30].

A strong statistical technique for experiment design and parameter optimisation is response surface methodology (RSM). Using process parameters, this can be utilized to create an accurate model for the response function in the optimal area [31]. Minimum quantity of research has been documented using RSM to optimize different ligands as parameters.

Our summary encompasses the accomplishments in the eco-friendly biotechnical preparation of Nickel nanoparticles and explores the influence of organic moieties to the physical characteristics of newly synthesized Ni-nanoparticles. Additionally, we present findings on the relative influence of various ligands using RSM, examining their structural effects and the biological properties of organically synthesized Nickel nanoparticles.

Methods

Chemical procurements

Chemicals are sourced from Sigma-Aldrich and employed in chemical reactions, with all solvents subjected to drying and additional purification through standard methods.

Synthesis of Ni complex

The compounds used in this study were obtained from the Department of Chemistry at the University of Rajasthan. The template condensation process was applied to produce Nickel (II) macrocyclic complexes, specifically utilizing benzyl dihydrazone with 3,4-pyridine dicarboxylic acid (ML_1) and 2,4-pyridine dicarboxylic acid (ML_2) in the presence of metal chloride. The synthesis followed established protocols as described in the literature. Subsequently, these complexes were further converted into nano-sized structures within our laboratory for their several applications. The illustrated macrocyclic structures are depicted in Fig. 1.

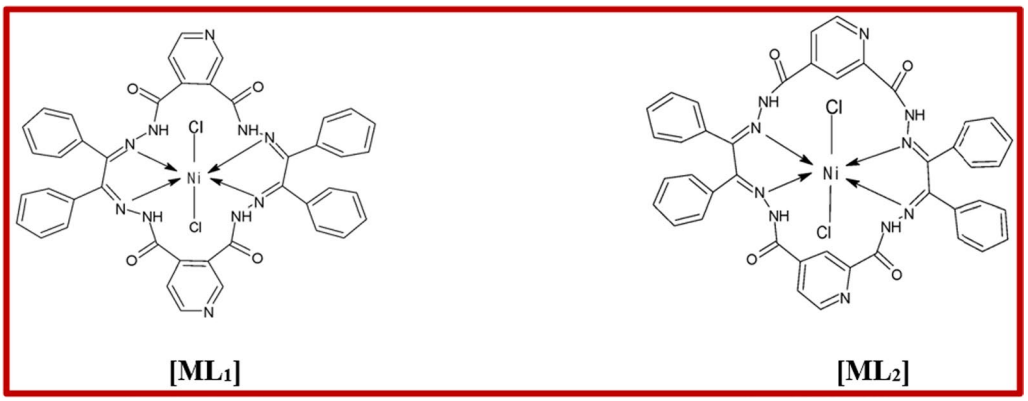


Fig. 1 Structures of the macro cyclic complexes

Preparation of plant extract

Macrotyloma uniflorum is acquired from the supermarket, cleaned with deionized H_2O, and drenched in distilled H_2O at 40 °C for 12 h. Subsequently, it undergoes a germination process for 48 h at 30 °C, with regular moistening using deionized H_2O every half day. The sprouts are then crushed to form a dense paste by incorporating phosphate buffer solutions (pH 8). The resultant blend is strained through a twin layer of whatman No.1 filter paper, and the filtrate was centrifuged at 12,000 rotations per minute for 8 min below 40 °C. The weightless floating liquid is collected, and the extract solution is employed for the reduction of compounds into nanoform (Fig. 2).

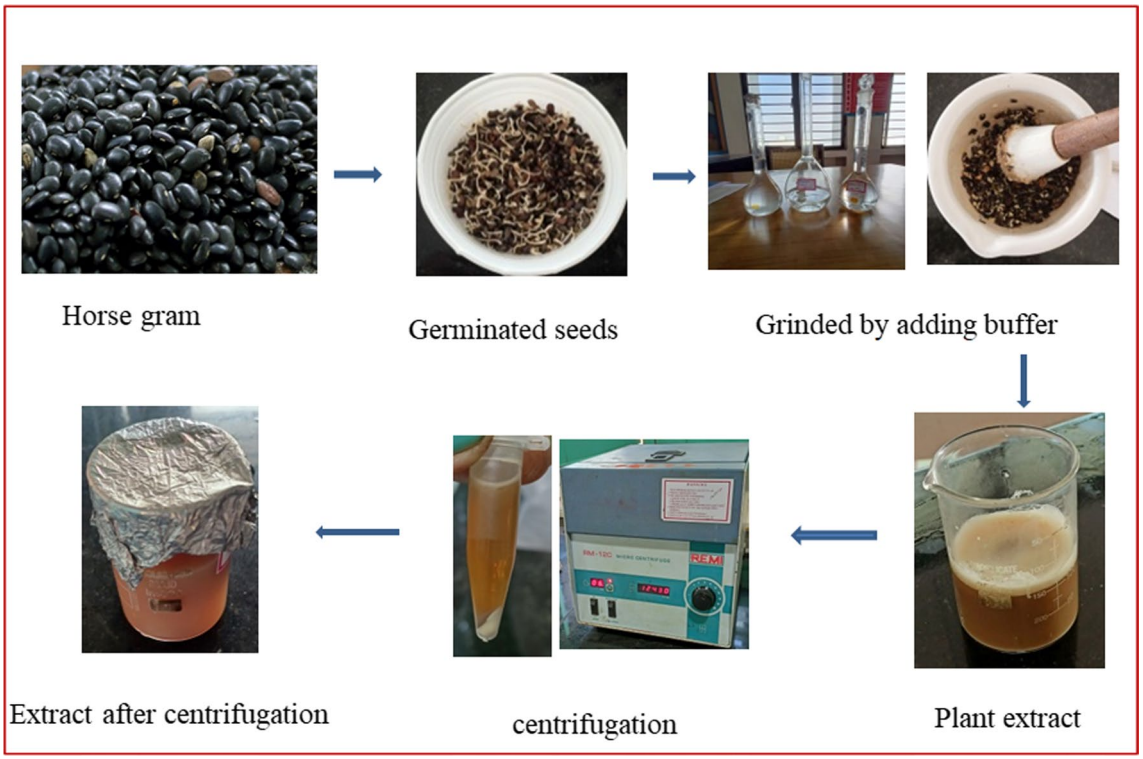


Fig. 2 Synthesis of extract of *Macrotyloma uniflorum*

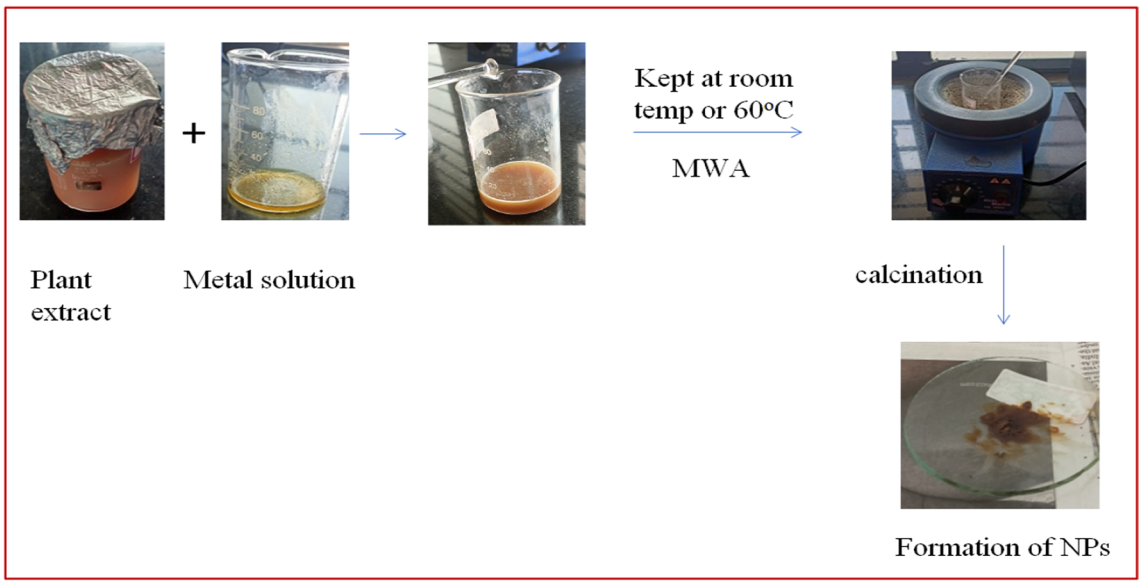


Fig. 3 Synthesis of Ni nanoparticles

Synthesis of Ni nanoparticles

The synthesis of Ni nanoparticles through a green route involves mixing the seed extract with the specific quantity of aqueous solution of nickel compounds, followed by allowing mixture to remain undisturbed until a noticeable colour change indicates nanoparticle formation. This process occurs either at room temperature or at 60–70 °C, depending on specific requirements.

For the microwave-assisted synthesis, a reduced amount of extraction solvent and a shorter reaction time yield efficient results. The reaction mixture is heated in a microwave at a power of 100–150 W for about 1–2 min. Later the extract undergoes centrifugation to room temperature, and the resulting precipitate is dried to obtain the desired metal nanoparticles. Notably, the percentage yield of nanoparticles from both synthesis methods was found to be nearly identical.

Utilizing an aqueous solution comprising plant material and Ni metal complexes in a 10:1 ratio, nanoparticles were synthesized following literature guidelines [32]. The mixture underwent incubation over a water bath, with careful pH control using 1 Normal H_3PO_4. Within 2–3 h, a distinct colour transformation from yellow to dark brown signified the conversion of the mixture into Nickel nanoparticles (Fig. 3).

The synthesized nanoparticles were subsequently subjected to electronic spectroscopy analysis. The size and crystallinity of Ni-nanoparticles were determined through XRD. The surface morphology of Ni-NPs was then examined using a scanning electron microscope (SEM) to obtain micro/nano-images of the complexes (ML_1 and ML_2). SEM analysis revealed that the Ni-nanoparticles exhibited a round shape within the nano size range. Furthermore, the nanoparticles have been evaluated for their anti-malignant action.

Statistical analysis (factorial design and optimization)

The experimental strategy, data scrutiny, and statistical optimization were carried out using Design-Expert software from Stat-Ease, USA. The objectives were to minimize the absorbance level in the sample, employing three variables: ML_1 with concentrations ranging from 0 to 60 µg/l(ppb), ML_2 the concentrations range from 0 to 60 µg/l, and temperature varying from 20 to 50 °C. These variables were explored at three levels, and the absorbance value was observed as the response.

Design-Expert software generated a 2^3 factorial design consisting of 20 experiments to systematically explore the parameter space. Table 1 presents the range and variables—both in actual and coded forms—that were

Table 1 Depiction of independent variable levels in both actual and coded formats

Variables (independent)	Signs	Levels of code		
		−1	0	+1
ML_1 concentration (µg/l)	X_1	0	30	60
ML_2 concentration (µg/l)	X_2	0	30	60
Temperature (°C)	X_3	20	35	50

investigated. Notably, the chosen mid-level values for ML_1 concentration, ML_2 concentration, and temperature were 30 µg/l, 30 µg/l, and 35 °C, respectively.

The outcomes of the experiments were displayed using a second-order polynomial equation.

$$Y = \beta_0 + \sum_{i=1}^{3} \beta_i X_i + \sum_{i=1}^{3} \beta_{ii} X_1^2 + \sum \sum_{i \neq j=1}^{3} \beta_{ij} X_i X_j \quad (1)$$

In the context of the regression equation, where Y denotes the anticipated value of the response variable and β denotes the coefficient, the outcomes were analysed using Design Expert. The influence of independent terms on dependent variables was evaluated, and through resolving the regression equation and scrutinizing the graphs, optimal conditions were determined. These optimal conditions were then employed to assess antioxidant and anticancer activities. The experimentally acquired responses were juxtaposed with the numerically predicted counterparts for comparison. To statistically assess the variance between mean values at a 95% confidence interval, analysis of variance (ANOVA) was employed. As per the quadratic model of ANOVA, the significance of model terms is signified by "Prob > F" values below 0.0500.

Antioxidant activity

Antioxidant estimation employs the use of 2, 2-Diphenyl-1-picrylhydrazyl (DPPH), a compound that aids in assessing the radical capacities of antioxidants [33]. The assessment relies on the capacity of antioxidants to diminish DPPH, measured through the DPPH radical assay principle. This involves determining the reduction in optical density (Abs) at 517 nm using a spectrophotometer after the interaction with nanoparticles (NPs). The reduction in DPPH colour during the reaction is tracked, and the antioxidant assay is computed through spectrometric analysis. The percentage of DPPH radical scavenging is calculated using the equation provided below [34].

The DPPH scavenging percentage is determined using the following formula:

$$\text{DPPH scavenging}(\%) = 100 \times \frac{\text{Absorbance of control} - \text{Absorbance of sample}}{\text{Absorbance of control}}$$

Here Absorbance of control represents the absorbance before adding test sample to DPPH and Absorbance of sample is the absorbance after reaction has taken place between *DPPH* and test sample.

The formula quantifies the reduction in absorbance due to the scavenging activity of the tested sample against the DPPH radical.

Anticancer activity

Upon procurement of cell lines from NCCS, Pune, the cells were maintained in DMEM augmented with 10% Fetal Bovine Serum (FBS) with antibiotic drugs (0.5 mL^{-1} penicillin/streptomycin) at 38 °C in a 4–5% CO_2/97% air atmosphere. To examine the MTT assay, cells were planted in a 96-well plate at a density of 5.0×10^3 cells/well in 100 µL of culture and allowed to incubate for 8–12 h at 35–40 °C, as previously documented [35]. To assess cell viability, three independent triplicate experiments was conducted three times using six concentrations of test chemicals ranging from 5 to100 µg/mL. After 24 h of incubation, each treatment was removed, and fresh media with varying concentrations of test compounds were added. Subsequently, the test solution was replaced with fresh media containing MTT solution (0.5 mg/mL), and the plates were further incubated at 35–37 °C for three hours. Following the reduction of MTT salt to chromophore formazan crystals, a precipitate was formed at the end of the incubation period. This conversion was facilitated by cells with metabolically active mitochondria. The absorbance of solubilized crystals in DMSO was then measured at 560 nm using a microplate reader.

$$\%\text{Inhibition} = \frac{100 \times (\text{Control} - \text{Treatment})}{\text{Control}}$$

Characterization of nanoparticles

The prepared samples underwent characterization using various analytical techniques. UV–visible spectroscopy was carried out using a UV1800S instrument from Shimadzu, Japan. SEM analysis was performed using a JEM-IT 800 SHL version, Japan. Fourier-transform infrared (FTIR) analysis was conducted using an Alpha-T instrument from Bruker. X-ray diffraction (XRD) analysis was accomplished using the X'Pert PRO XRD PW 3040 system.

Results

IR-spectroscopy

IR spectroscopy offers high reliability in characterizing the bulk of nanoparticles. By estimating vibrations of

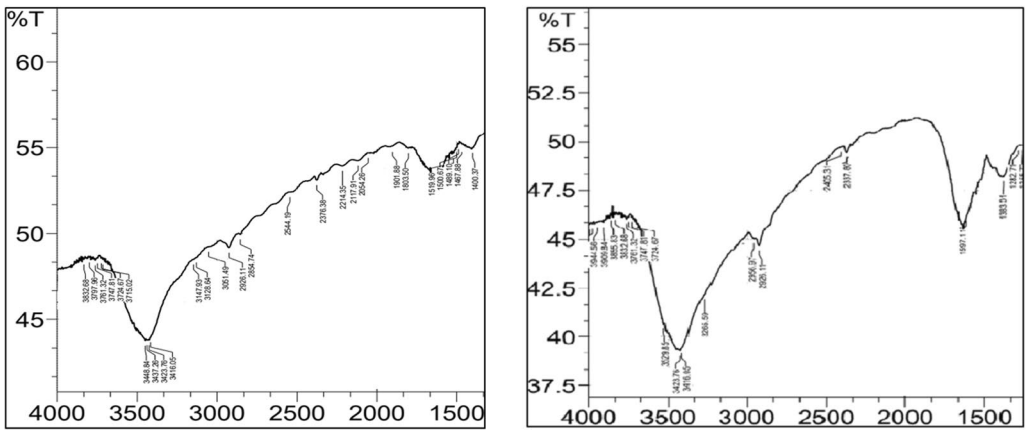


Fig. 4 IR-spectra of Ni-NPs of ML_1 and ML_2

functional groups on their surface, FTIR, in particular, is incredibly versatile for surface analysis of nanoparticles in specific conditions, enabling determination of their surface chemical composition with precision.

The IR spectra analysis of both metal nanoparticle complexes was conducted to elucidate their structural features and bonding interactions. Remarkably, the spectra of the complexes show absence of bands corresponding to ν_{as} ($-NH_2$) at 3360 cm^{-1}, ν_{as} ($-NH_2$) at 3280 cm^{-1}, and ν (C=O) with the range of 1680–1690 cm^{-1}. This absence in the spectra indicates the condensation process and the construction of a macrocyclic structure. Peaks observed in the vicinity of 1648–1580 cm^{-1} were accredited to ν(C=N). The band position for ν(C=N) was found to be lower than the typical values associated with azomethine groups, supporting the inference of coordination of the group with the metal atom and the creation of macrocyclic complexes. Furthermore, the absorption bands corresponding to the phenyl ring were identified in the regions of 1465–1495 cm^{-1} and 1355–1390 cm^{-1}, assigned to $\nu_{asym}C_6H_5$ and $\nu_{sym}C_6H_5$, respectively (Fig. 4).

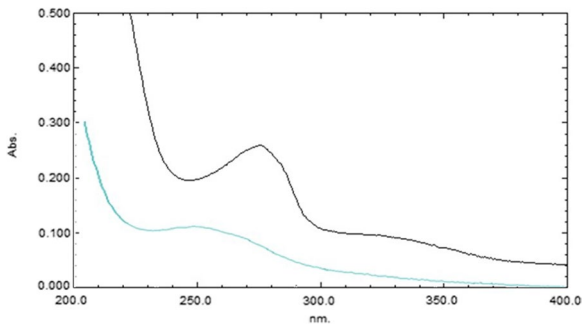


Fig. 5 UV–Vis spectra of Ni-NPs of ML_1 and ML_2

Electronic spectra of Ni-NPs

UV–Visible spectroscopy is a powerful method for studying the growth of metal nanoparticles within a polymer network or the formation of a polymer network around a metal nanoparticle core. UV–Visible spectroscopy is commonly employed to investigate the plasmonic resonance of nanoparticles. By analysing absorbance data in the range of 200–700 nm, we have confirmed the formation of Ni nanoparticles and their plasmonic resonance. This enables us to characterize and confirm the presence of reduced Ni metal in the form of nanoparticles.

The observation of electron oscillation points to the occurrence of surface plasmon resonance (SPR), where absorption bands are evident. The phenomenon arises from the absorption of UV light by Ni-NPs, leading to consistent oscillation of conduction electrons. This resonance is achieved when the frequency of surface electrons of metal NPs aligns with that of incident photons. The UV–Visible spectrophotometer is employed to analyse the optical density of the absorbed light [36] (Fig. 5).

XRD analysis

X-ray diffraction (XRD) is a technique utilized to analyse the crystalline properties of materials, providing insights into their structural characteristics, phase nature, lattice parameters, and grain size. The lattice parameter is determined through the application of the Scherrer equation, which involves assessing the broadening of the most prominent peak observed in an XRD pattern for a given sample.

The XRD spectra of Nickel-nanoparticles, synthesized through the reduction of Ni metal complexes

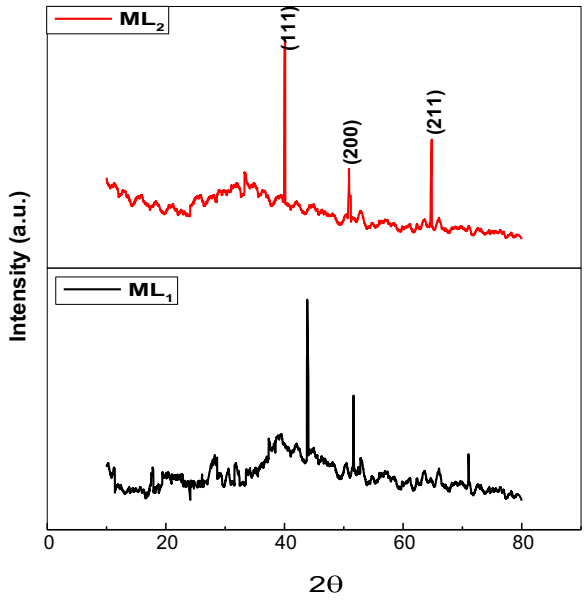


Fig. 6 XRD spectra of Ni-NPs of ML_1 and ML_2

(ML_1 and ML_2) using the seed extract of *Macrotyloma uniflorum*, were examined. For the nano-particles of ML_1 compound, five unique diffraction peaks were identified with corresponding 2θ values of 18.85, 20.56, 22.55, 17.65, and 16.17. Particularly, the peak at 18.85° exhibited the maximum intensity. Similarly, the XRD spectrum of the ML_2 compound displayed six characteristic diffraction peaks at 2θ values of 31.13, 22.38, 19.82, 25.1, 27.3, and 16.5, with the peak at 31.13° demonstrating the highest intensity (Fig. 6).

SEM (scanning electron microscope) of nickel-NPs

SEM is a powerful technique used for analysing particle characteristics, such as size, shape, and texture with high precision. Operating with only small amounts of material, typically in the milligram range, SEM employs a focused electron beam that scans the prepared sample in a series of parallel tracks. Figures 7 and 8 depict SEM images of two distinct metal nanoparticles.

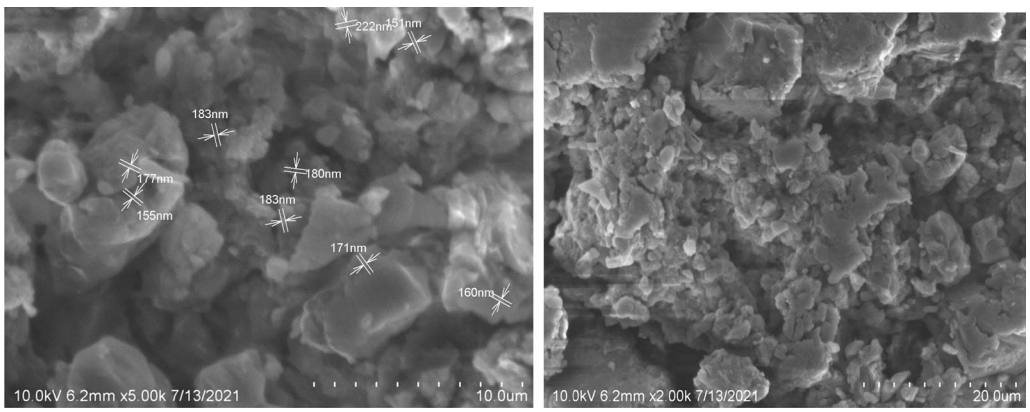


Fig. 7 SEM images of ML_1 NPs

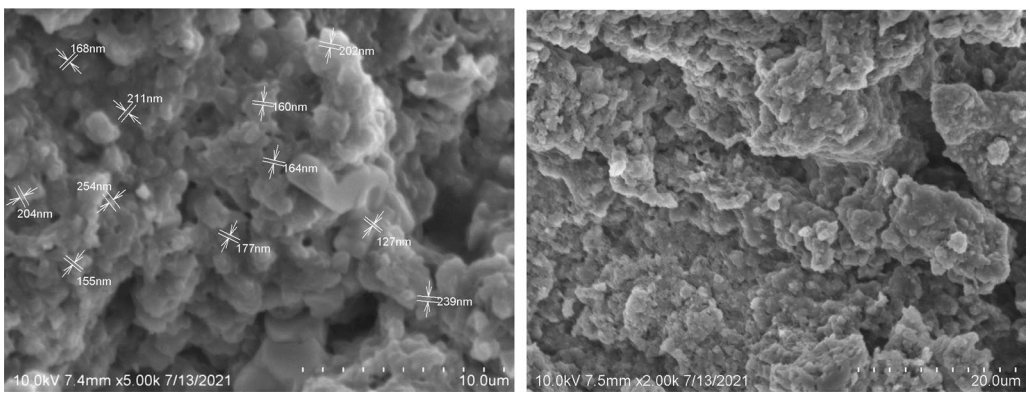


Fig. 8 SEM images of ML_2 NPs

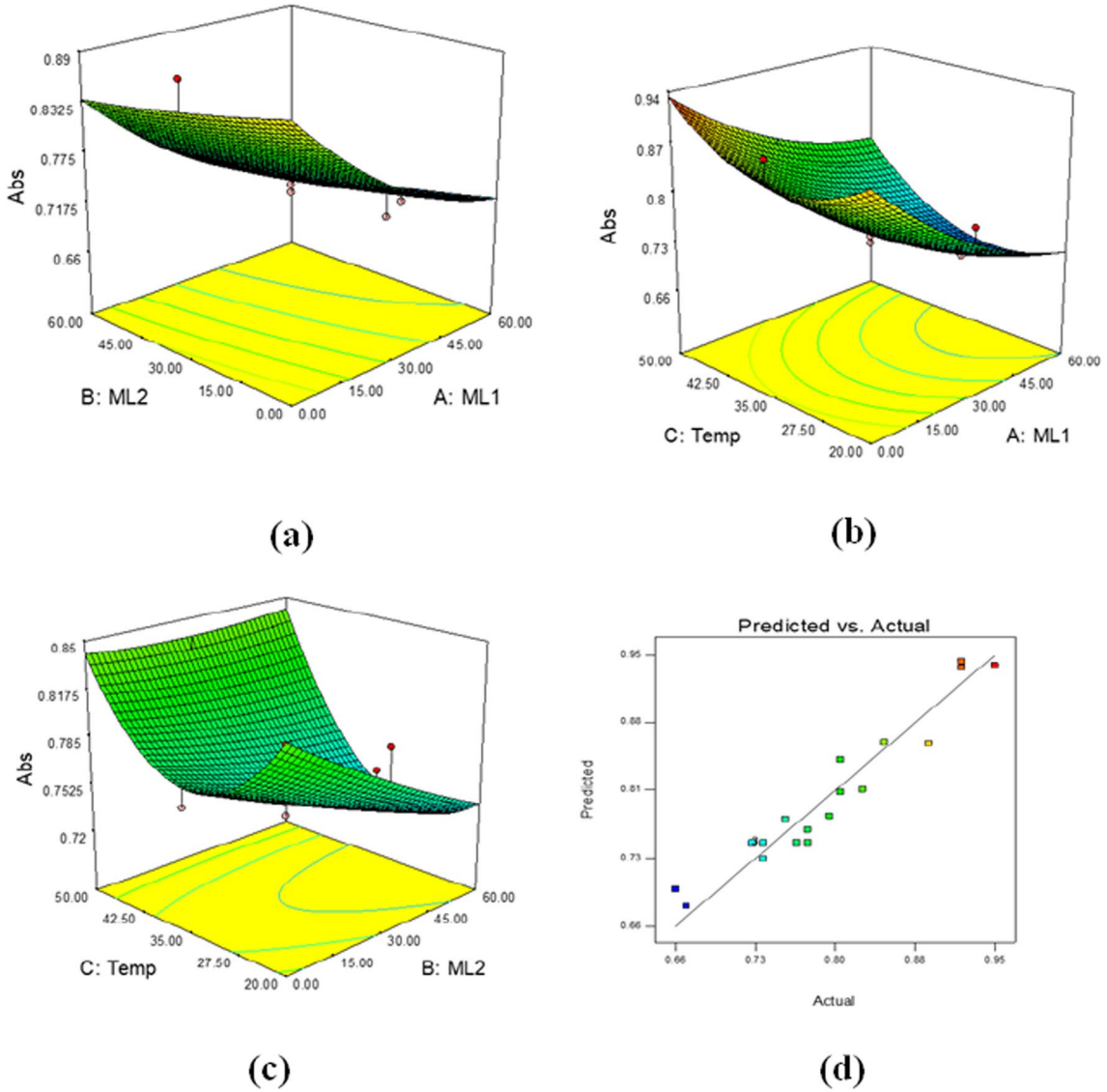


Fig. 9 **a** 3D plot for absorbance as a function of ML_1 and ML_2 concentration. **b** 3D plot for absorbance as a function of ML_1 concentration and temperature. **c** 3D plot for absorbance as a function of ML_2 concentration and temperature. **d** Predicted versus actual values of absorbance

Statistical analysis using response surface methodology

Response surface methodology (RSM) stands out as a highly efficient technique within the realm of design of experiments (DOE). Its primary goal is to streamline the optimization of crucial parameters to achieve an optimal response while ensuring a robust model fit. By employing RSM, we have effectively optimize key factors such as ML_1 concentration, ML_2 concentration, and temperature, all while conducting a limited number of experiments (20). This approach is particularly advantageous as it avoids the need for an extensive array of experiments (Figs. 9).

The design table was obtained (Table 2) and experiments were conducted following the conditions of the table. The absorbance was measured and a quadratic model with 20 runs was built. It was investigated how design process parameters affected absorbance.

In this context, key model terms include ML_1 and ML_2 concentrations, temperature, and the interaction term involving temperature. The model's importance is substantiated by an *F*-value of 15.05. Furthermore, the "Lack of Fit *F*-value" of 3.18 suggests that the lack of fit is not significantly different from pure error, underscoring the adequacy of the model. This signifies that the

Table 2 Central composite design of input variables with responses

S. no	Independent variables			Response	
	Factor 1 (ML_1, µg/l)	Factor 2 (ML_2, µg/l)	Factor 3 (Temperature, °C)	Experimental (Absorbance)	Predicted (Absorbance)
1	60.00	30.00	35.00	0.66	0.7
2	30.00	60.00	35.00	0.74	0.75
3	0.00	0.00	20.00	0.92	0.94
4	30.00	30.00	50.00	0.81	0.807
5	30.00	30.00	35.00	0.74	0.75
6	30.00	30.00	35.00	0.74	0.75
7	0.00	60.00	50.00	0.92	0.94
8	60.00	0.00	50.00	0.81	0.84
9	60.00	60.00	50.00	0.83	0.81
10	0.00	60.00	20.00	0.85	0.86
11	30.00	30.00	35.00	0.73	0.75
12	60.00	60.00	20.00	0.67	0.68
13	30.00	30.00	35.00	0.78	0.76
14	30.00	30.00	35.00	0.77	0.75
15	30.00	30.00	20.00	0.80	0.78
16	0.00	30.00	35.00	0.89	0.86
17	0.00	0.00	50.00	0.95	0.94
18	60.00	0.00	20.00	0.78	0.75
19	30.00	0.00	35.00	0.76	0.77
20	30.00	30.00	35.00	0.74	0.738

model fits the data well. This indicates a good fit of the model to the data. The coefficient of determination (R^2) for the response is 93%, affirming the appropriateness of the applied models. The adjusted coefficient of determination (Adj. R^2) for the response is determined to be 86%. As a result, it can be said that the experimental value meets Eq. (2) and the regression coefficients fit into a second-order polynomial equation.

$$Y = 1.209 - 0.00546x_1 - 0.00267x_2 - 0.01855x_3 + 1.388 \times 10^{-6}x_1x_2 + 2.5 \times 10^{-5}x_1x_3 + 4.722 \times 10^{-5}x_2x_3 + 3.232 \times 10^{-5}x_1^2 + 4.545 \times 10^{-6}x_2^2 + 2.626 \times 10^{-4}x_3^2 \quad (2)$$

In the given equation, where Y represents absorbance, x_1 stands for ML_1 concentration, x_2 for ML_2 concentration, and x_3 for temperature; it is noteworthy that concentration of ML_1 and ML_2 as well as temperature all exhibit a negative impact on absorbance. In order to explore the impact of interactions, 3D plots were created by graphing absorbance versus independent variables while maintaining optimal circumstances for the other variables. These graphs effectively interpreted the interactions between the two factors.

Variables optimization and experimental validation

To guarantee the precision and dependability of the formulated model, experiments were conducted to compare predicted and actual responses, as shown in Fig. 11. Once validated, the model was employed to optimize conditions for maximum antioxidant and anticancer activities. As depicted in Fig. 10a, an increase in ML_1 concentration up to approximately 40 µg/l resulted in a decrease in absorbance. This suggests that higher concentrations of ML_1 may induce cytotoxic effects on the cells, leading to a decline in cell viability, reflected by lower absorbance measurements and further increases in ML_1 concentration did not

Fig. 10 Preparation of DPPH solution and DPPH with Ni-NPs solution

Table 3 Analysis of variance with the second order polynomial fit equation

Source	Sum of squares	DF	Mean square	*F* value	*p* Value
Model	0.11	9.0	0.013	15.05	0.0001
Residual	0.008355	10.0	0.0008355		
Lack of fit	0.006355	5.0	0.001271	3.18	0.1151
Pure error	0.002	5.0	0.0004		
Total	0.12	19.0			

significantly affect absorbance. Conversely, the increase in ML_2 concentration did not exhibit a notable change in absorbance, possibly indicating that ML_2 concentration had already reached its saturation point (Table 3).

Antioxidant activity

To quantify the antioxidant potential of the Ni NPs, 2 ml volume of a methanol-dissolved 100 µM DPPH solution was combined with 2 ml of diverse concentrations of Ni NPs solution. The resultant mixture was left undisturbed at room temperature for 30 min. Following this, the absorption at 520 nm for the samples was measured utilizing a spectrophotometer (Figs. 10, 11, 12). The antioxidant activity was subsequently calculated using the provided formula. The calculation of IC_{50} value of ML_1 and ML_2 (NPs) in DPPH assay is given in Table 4 and 5.

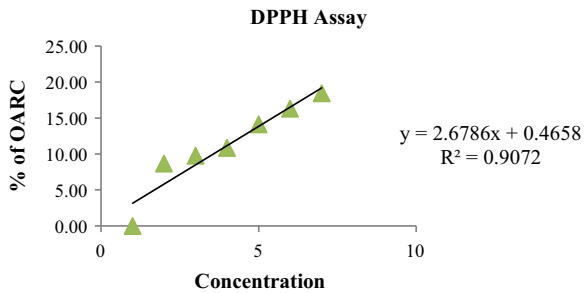


Fig. 11 Assessment of the scavenging activity of ML_1 (NPs) against DPPH radicals

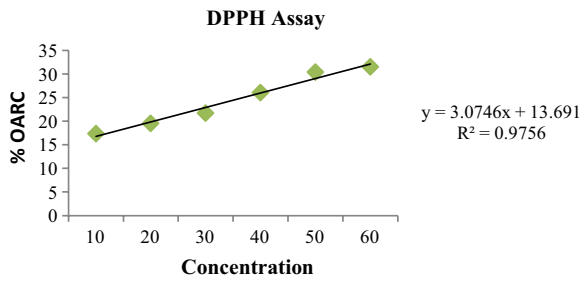


Fig. 12 Assessment of the scavenging activity of ML_2 (NPs) against DPPH radicals

Table 4 IC_{50} value of ML_1 (NPs) in DPPH assay

S. no	Concentration of the sample(µg/ml)	Absorbance	% of OARC	IC50
1	Blank	0.92	0.00	19.33
2	10	0.84	8.70	
3	20	0.83	9.78	
4	30	0.82	10.87	
5	40	0.79	14.13	
6	50	0.77	16.30	
7	60	0.75	18.48	

Table 5 IC_{50} value of ML_2 (NPs) in DPPH assay

S. no	Concentration of the sample (µg/ml)	Absorbance	% of OARC	IC50
1	Blank	0.92	0	10.49
2	10	0.76	17.39	
3	20	0.74	19.56	
4	30	0.72	21.73	
5	40	0.68	26.08	
6	50	0.64	30.43	
7	60	0.63	31.52	

$$\%\ \text{of DPPH free radical scavenging} = \frac{\text{Blank} - \text{Test sample}}{\text{Blank}} \times 100$$

Cytotoxic activity

Assessing the cytotoxicity of the synthesized compounds against HeLa (cervical) and A549 (lung) cancer cell lines involved evaluating the number of viable cells remaining after a specific incubation period with macrocyclic complexes. The in-vitro cytotoxic activity results were quantified as IC_{50} values, representing the concentration of the compound in µg/mL that inhibits cell proliferation by 50% compared to untreated control cells is also summarized. The macrocyclic complexes exhibited a dose-dependent impact on the viability of both types of cancer cell lines (Figs. 13, 14, 15, 16). The growth inhibition percentage of cancer cell lines demonstrated an increase with the rising concentration of the tested compounds (Table 6).

The statistical analysis of MTT cytotoxicity study data reveals noteworthy findings regarding the cytotoxic potential of test compounds ML_1 and ML_2 against A549 and HeLa cell lines. In the case of A549 cell lines, both ML_1 and ML_2 exhibit significant cytotoxicity, with IC_{50} concentrations of 44 µg/mL and 31.20 µg/mL,

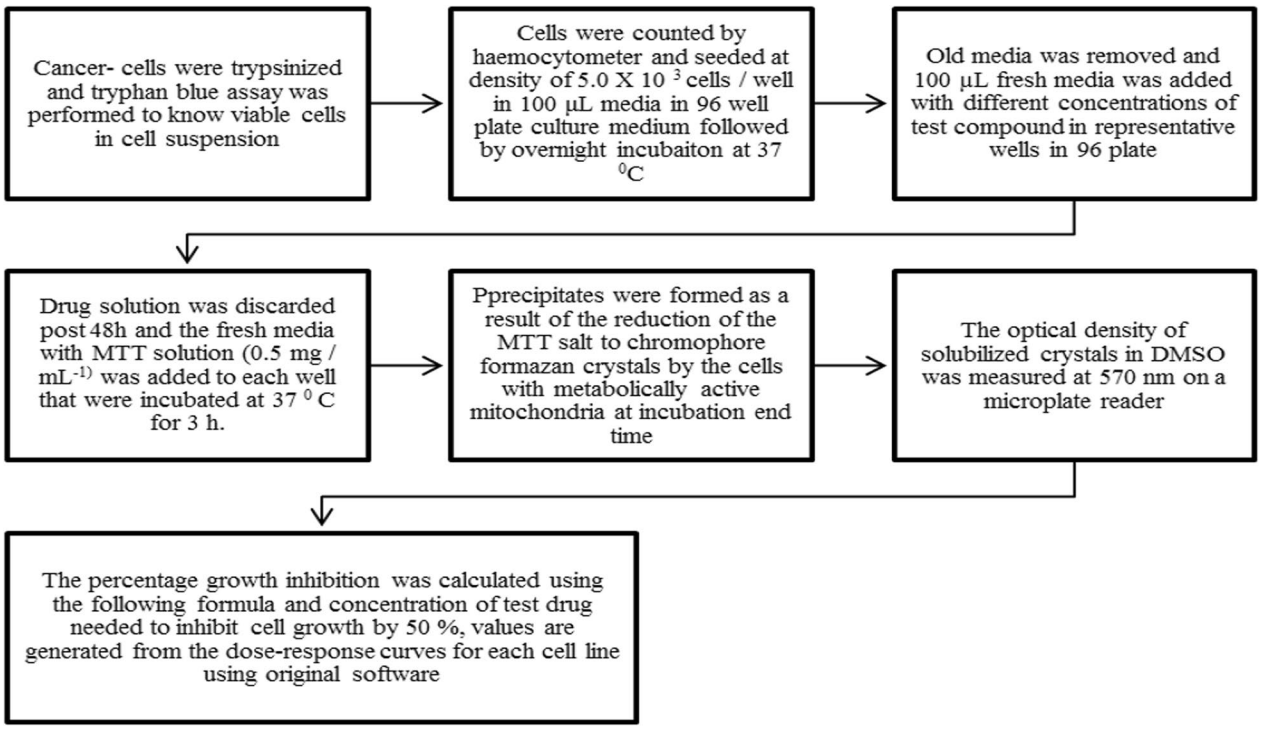
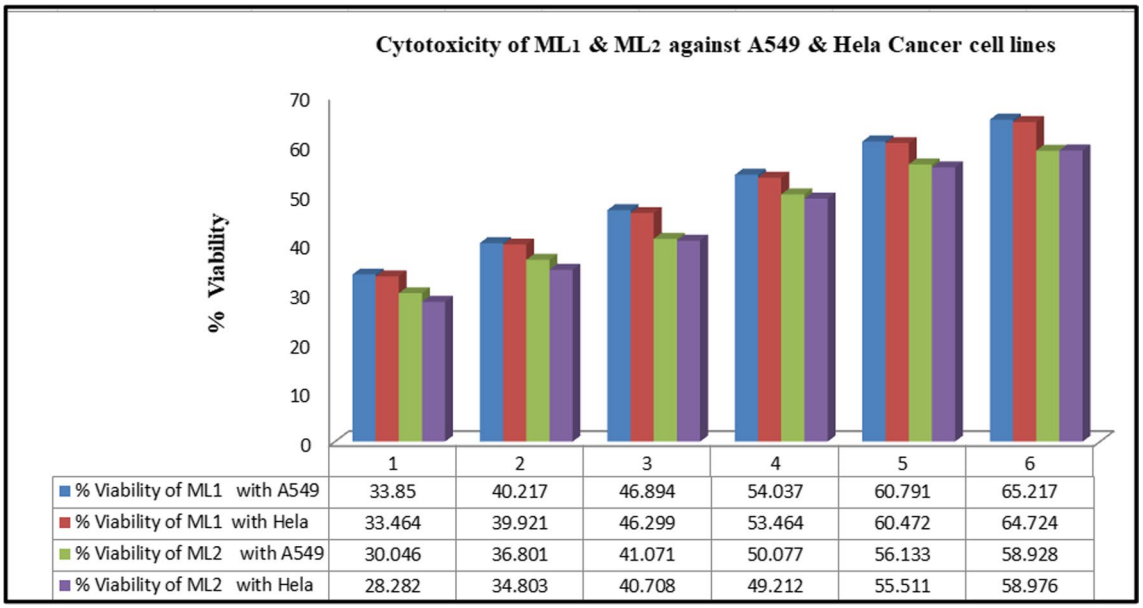


Fig. 13 Flow diagram showing the route of complete anticancer activity



	1	2	3	4	5	6
% Viability of ML1 with A549	33.85	40.217	46.894	54.037	60.791	65.217
% Viability of ML1 with Hela	33.464	39.921	46.299	53.464	60.472	64.724
% Viability of ML2 with A549	30.046	36.801	41.071	50.077	56.133	58.928
% Viability of ML2 with Hela	28.282	34.803	40.708	49.212	55.511	58.976

Fig. 14 Bar diagram showing the % Viability and Cytotoxicity of ML_1 and ML_2 against A549 and Hela Cancer cell lines

respectively. Markedly, ML_2 stands out for its substantial cytotoxicity against HeLa cells, suggesting its potential as a potent anti-lung cancer agent, given its low IC_{50}. Similarly, against HeLa cell lines, ML_1 and ML_2 demonstrate substantial cytotoxic potential, displaying IC_{50} concentrations of 43.37 µg/mL and 21.42 µg/mL, respectively.

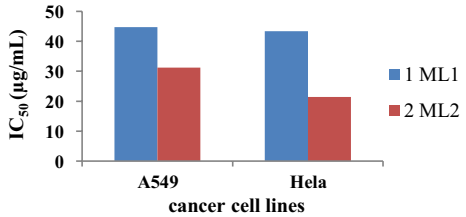


Fig. 15 IC_{50} values of Ni-NP against A549 and HeLa cell lines

Discussions

All the characterization techniques we have utilized have effectively provided valuable insights into the newly synthesized nanoparticles. The infrared (IR) spectral data offered valuable information about presence of function groups, the structural modifications and bonding configurations within the synthesized macrocyclic complexes. In UV–visible studies, the size and dispersion of nanoparticles (NPs) significantly influence the characteristics, breadth, and position of the surface plasmon resonance (SPR) peak observed. The UV–Visible spectrophotometer data within the 250–300 nm range for the synthesized Ni-NPs reveals their plasmonic nature, signifying electron oscillation. This emphasizes the pivotal role of NP size and distribution in shaping the optical properties and behaviour of synthesized Ni-NPs. X-ray diffraction (XRD) analysis findings offer valuable insights into the structure and size distribution of the synthesized Ni-NPs, thereby informing their potential applications across various domains. Utilizing the Debye–Scherrer formula, particle sizes for both ML_1 and ML_2 compounds were determined to fall within the nano-range. Scanning electron microscopy (SEM) enables a meticulous examination of nanoparticle boundaries, enhancing precision in assessing nanoparticle size and distribution. The images obtained by the Scanning Electron Microscope for Ni-NPs of metal complexes (ML_1 and ML_2) approve that the nanoparticles are almost spherical in form with the size of maximum 170 nm. Response surface methodology (RSM) studies reveal a notable trend wherein as temperature rises to approximately 30 °C, absorbance initially decreases before rising again. This temperature sensitivity underscores its crucial role in optimizing results. The most favourable outcomes were achieved when experimentally validated data were fitted into the equation, yielding a minimum absorbance of 0.73 at ML_1 concentration of 35 µg/l, ML_2 concentration of 15 µg/l, and a temperature of 30 °C, closely aligning with the predicted response.

The antioxidant radical-scavenging potential of Ni NPs was evaluated using a methanolic solution

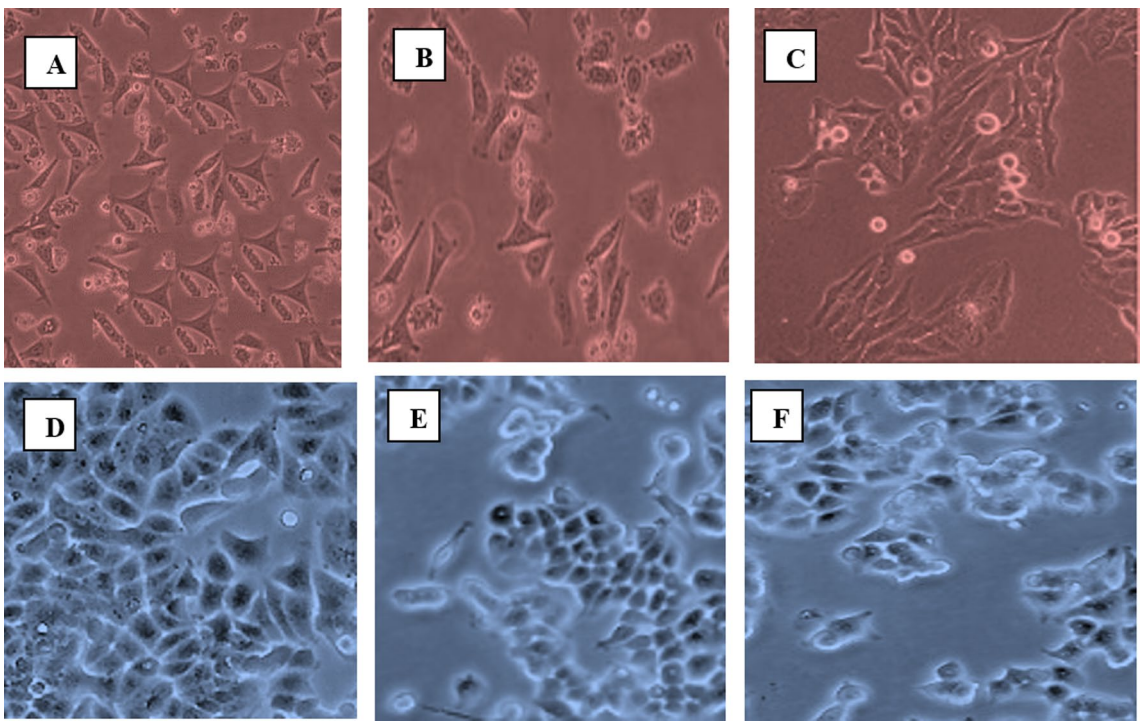


Fig. 16 **A** HeLa cell line-control. **B**, **C** Variations in the morphology of HeLa cell line after exposure to NPs of ML_1 and ML_2. **D** A549 cell line-control. **E**, **F** Variations in the morphology of A549 cell line following exposure to NPs of ML_1 and ML_2

Table 6 IC_{50} Comparison of ML_1, ML_2 Compounds against A549 and HeLa cell Lines after 24-Hour Incubation: MTT Study

S. no	Compound IC50 (ug/L)		
		A549	Hela
1	ML_1	44.76	43.37
2	ML_2	31.2	21.42

containing 2,2-diphenyl-1-picrylhydrazyl (DPPH), a well-known radical and scavenger for other radicals. Initially, the methanolic DPPH solution exhibits a deep violet colour, which transitions to colourless or fades to a pale yellow upon neutralization with antioxidants, indicating a reduction reaction and confirming the radical nature of the test sample. The calculations of IC_{50} values for both nanoparticles in the DPPH assay indicate that ML_2 exhibits greater antioxidant potential compared to ML_1. The anticancer activity results indicated that all the complexes exhibited moderate to good anticancer activity against both HeLa and A549 cancer cell lines. In summary, both ML_1 and ML_2 demonstrate effective cytotoxicity against human lung and cervix cancer cells, positioning them as promising candidates for further exploration in cancer therapeutics. ML_2, in particular, emerges as a potent anti-cervix cancer agent, characterized by its low IC_{50} value.

Conclusions

Researchers, prompted by the toxicity and side effects associated with cisplatin, are exploring alternative approaches for developing transition metal-based anticancer agents. The cytotoxic potential of nickel nanoparticles (Ni-NPs) has been thoroughly investigated using cervical and lung cancer cell lines. In this study, the utilization of Horse Gram seed extract *(Macrotyloma uniflorum)* has revealed its richness in phenolic and flavonoid compounds, well-documented for their potent antioxidant activity in existing literature. The experiments were structured to investigate the impacts of diverse factors, and the utilization of Response Surface Methodology proved effective for optimization. Following computation, the regression coefficients were incorporated into a second-order polynomial equation for fitting. The experimental and predicted values agree closely which validates the model. Moreover, the application of *Macrotyloma uniflorum*-mediated Ni-NPs has demonstrated an enhanced anticancer effect against HeLa and A549 cell lines responded in a manner dependent on the concentration. The mechanism underlying the deactivation of cancer cell lines aligns with existing literature, attributing it to intra-cellular nucleus damage. An additional noteworthy observation indicates that Nickel metal NPs with 2,4-dicarboxylic acid (ML_2) as a ligand exhibit a more significant impact on antioxidant and anticancer activities compared to their counterparts with 3,4-dicarboxylic acid (ML_1) as the ligand moiety. This difference in impact may be attributed to the method employed to convert metal complexes into metal-NPs. The current research underscores the possibility of refining the bio-toxicity and biochemical properties of Ni-NPs to develop a new generation of versatile anticancer agents with clinically proven efficiency. Remarkably, the predicted data aligns closely with experimental results, affirming the reliability and credibility of RSM (Response Surface Methodology) model for studying anticancer and antioxidant properties in this context.

Abbreviations

ML_1	Nickel metal NPs with 2, 4-dicarboxylic acid (ML_2) as a ligand
ML_2	Nickel metal NPs with 3, 4-dicarboxylic acid (ML_2) as a ligand
DPPH	2, 2-Diphenyl-1-picrylhydrazyl
MTT	3-[4,5-Dimethylthiazol-2-yl]-2,5 diphenyl tetrazolium bromide
SEM	Scanning electron microscope
RSM	Response surface methodology

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s43094-024-00618-0.

Additional file 1. Four tables of statistical data are being provided for Anti-cancer studies.

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Author contributions

SA conducted a comprehensive literature review focusing on organically Nano-Fabricated Ni metal complexes, exploring their antioxidant and anticancer activities, and conducted characterization and activity assessments. SB coordinated the development of the initial draft of the article. MVM enhanced the writing style and participated in the proofreading process. The final manuscript was reviewed and approved by all authors.

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Availability of data and materials

Upon request, the data and materials can be made available.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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