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Waste-to-Value Biotechnology: Engineering Microbial Cell Factories for Circular Conversion of Agro-Industrial Residues into High-Value Bioproducts

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ABSTRACT: The residues from agriculture, food industry, sugar and starch milling, oilseeds crushing, and dairy industry represent a considerable source of fermentable carbon, nitrogen, and other bioactive molecules, but their potential remains poorly exploited due to the absence of economic viability in conventional treatment technologies. Microbial cell factories, including both natural strains and strains with metabolic modification via synthetic biology tools, offer a biological way to turn such heterogeneous streams into biofuels, biopolymers, enzymes, organic acids, biosurfactants, single-cell protein, and bioactive molecules. This review aims to compile recent advancements within the pathway from waste to value through agro-industrial residues characterization, pretreatments, microbes' selection, metabolic/synthetic biology engineering and ending up with product diversity and sustainability evaluation. Feedstock-microbe-process compatibility emerges as an overarching challenge in the field with current gaps observed in feedstock heterogeneity management, stability, costs for downstream process, and techno-economic/life cycle analysis. Artificial intelligence-assisted methods and genome scale modelling tools expected to be utilized in future are also mentioned.

1. INTRODUCTION

The generation of both solid and liquid wastes in the global agro-industry reaches billions of tonnes per year as a result of harvesting of agricultural crops, processing of cereals, extraction of sugar and starch, oilseed pressing, fruit and vegetable processing, and dairy production. The annual production of agricultural biomass in the European Union is estimated to be

around 900 million tonnes, a considerable amount of which includes crop wastes, and similar quantities occur in leading agro-regions of Asia and America.[1,4]

These wastes cause not only ecological but economic damage if left without proper treatment because their decomposition produces greenhouse gases, their leachates pollute both soil and water, and their combustion during the burning of crop waste deteriorates the air quality in the region. On the other hand, the majority of these agro-industrial residues possesses a significant biotechnological potential, being highly abundant in such biomolecules as cellulose, hemicellulose, starch, sugar, proteins, lipids, and phenolic compounds from lignin.[1,4]

The conventional methods of waste treatment, namely landfilling, incineration, and simple composting, have been devised to manage volume and alleviate any imminent risks to human health rather than recovering chemicals. Waste valorization changes the goal completely; the agro-industrial wastes are seen as raw materials, while the design of processes aims at maximizing value recovery from them. The biological pathways usually proceed at milder temperatures and pressures, are flexible in terms of variability in feedstock composition, and are adjustable with respect to desired products through strain and process engineering.[1,4]

Microbial cell factory is a term used to refer to a microorganism which has been chosen, genetically altered or engineered in such a way that it has the ability to convert a specific raw material into a desired end product by the use of processes that are usable in an industrial set up. Naturally existing producers have most of the equipment for waste conversion, but engineered producers expand their reach.[4]

Most of the papers on valorization of waste through biological means are confined to feedstock- or product-specific systems and provide results about increased yields in a single combination of waste residue, microorganism, and product but neglect the general problem of compatibility of the system because of the nature of the feedstocks being heterogeneous and seasonal. In this review, the existing literature is discussed in the context of the entire conversion process, which includes feedstock classification, feedstock pretreatment, selection of microorganism, metabolic engineering of microorganisms, diversification of products, and sustainability analysis, keeping the compatibility issue at its center.[1]

This review is based on peer-reviewed literature that is mainly available from 2018-2026 from Scopus, Web of Science, PubMed, Science Direct, and Google Scholar databases through the use of the following keywords: "agro-industrial waste," "valorization of waste," "microbial cell factory," "metabolic engineering," "adaptive laboratory evolution," "biorefinery," and product class names (bioethanol, polyhydroxyalkanoate, biosurfactant, organic acid, single-cell protein). Priority was given to those studies that have involved the bioconversion of true or close-to-true agro-industrial wastes than model substances, and information is organized by themes along the feedstock to product process chain.[1]



Fig. 1: Overall conceptual framework of waste-to-value biotechnology, from agro-industrial residues to circular bioeconomy integration.

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2. AGRO-INDUSTRIAL RESIDUES: COMPOSITION, DIVERSITY AND BIOTECHNOLOGICAL POTENTIAL

Residues from agro-industries can be broadly categorized on the basis of their source in the agricultural value chain, namely, crop residues (straw, stover, husk, bagasse), residues from fruit/vegetable processing (peels, pomace, seeds), sugar/starch industry residues (molasses, bagasse, cassava peel), residues from oilseed processing (oil cakes, meal, bleached earth), and residues from the dairy industry (whey, buttermilk). The residues can be further classified according to the time period they are generated: first-generation residues comprising starch/sugar/oil-containing residues from food crops, second-generation lignocellulosic residues obtained from non-food crop parts, and third-generation residues from algal/aquatic biomass processing.[1,4]

The biotechnological potential of the residue will depend upon its macromolecular composition. Residues containing carbohydrates (molasses, whey permeate, starch-containing peels) contain easily fermentable sugars; lignocellulosic residues contain cellulose/hemicellulose that have to be hydrolyzed before they can be fermented, in addition to a recalcitrant fraction of lignin; oil cakes/waste cooking oils yield lipids for the production of single-cell oils, biosurfactants, or polyhydroxyalkanoates; and proteinaceous residues can be used as such or hydrolyzed to peptides and amino acids. In contrast to laboratory-substrate materials, there is considerable variation between the composition of such wastes depending on the type of crop, time of harvest, geographical source, storage, and pretreatment method employed prior to microbial processing, and this variation is one of the main reasons for the lack of portability of conversion results from one batch of residue to another.[1,4,8,9,10]

The practical choice of residue to be converted via microbes depends on many factors including availability throughout the year, good and consistent composition, low or even negative cost, easy procurement and transport, and integration with present industrial agriculture. Residues which meet all these requirements at once are molasses, whey, and lignocellulosic crop residues.[1,4]

To keep the organization of evidence consistent across this review, the five residue classes defined above (crop residues; fruit and vegetable residues; sugar and starch residues; oilseed residues; and dairy by-products) are used as the organizing framework. Table 1 links each class to its principal bioproduct potential, and the examples discussed in Sections 4 to 7, including the feedstock-to-product conversions in Table 3, are identified by the residue class from which the feedstock originates.

Feedstock characterization is a prerequisite for matching a residue to a microbial host and a process. The composition of structural carbohydrates (cellulose and hemicellulose), lignin, extractives, ash, protein and lipid, together with moisture content, determines the fermentable fraction, the pretreatment severity required and the likely inhibitor load, and standardized analytical procedures for biomass composition are available.[51,52] Composition alone does not fully explain feedstock behavior, however: physical and mechanical properties such as moisture, density, flowability, grindability and rheology also influence handling, continuous operation and conversion yield, and the wide variation in feedstock types and compositions makes it necessary to relate feedstock quality attributes to conversion performance.[51,53] The corresponding sugar, lipid and nitrogen profiles likewise determine the suitability of carbohydrate-rich (molasses, whey), lipid-rich (oil cakes, waste cooking oil) and protein-rich residues. Characterizing each residue lot before fermentation is therefore needed to interpret and compare conversion results between studies.

Table 1: Classification and composition of major agro-industrial residues and their principal bioproduct potential

Residue class	Representative examples	Major composition	Principal bioproduct potential
Crop residues	Rice straw, wheat straw, corn stover, sugarcane bagasse	Cellulose, hemicellulose, lignin	Bioethanol, organic acids, enzymes, single-cell protein. [4,48,50]
Fruit & vegetable waste	Citrus peel, pomace, seeds	Pectin, sugars, phenolics	Bioactive compounds, pigments, biogas, enzymes [2,24,30]
Sugar & starch residues	Molasses, cassava peel, potato peel	Sucrose, starch, residual sugars	Bioethanol, lactic acid, PHA, biosurfactants.[4,39,35]

Oilseed residues	Oil cakes, spent bleaching earth, waste cooking oil	Residual lipids, proteins	Single-cell oils, biodiesel precursors, biosurfactants[8,10,11,35]
Dairy by-products	Whey, whey permeate, buttermilk	Lactose, whey proteins	Lactic acid, bacterial cellulose, whey protein hydrolysates [47,24]

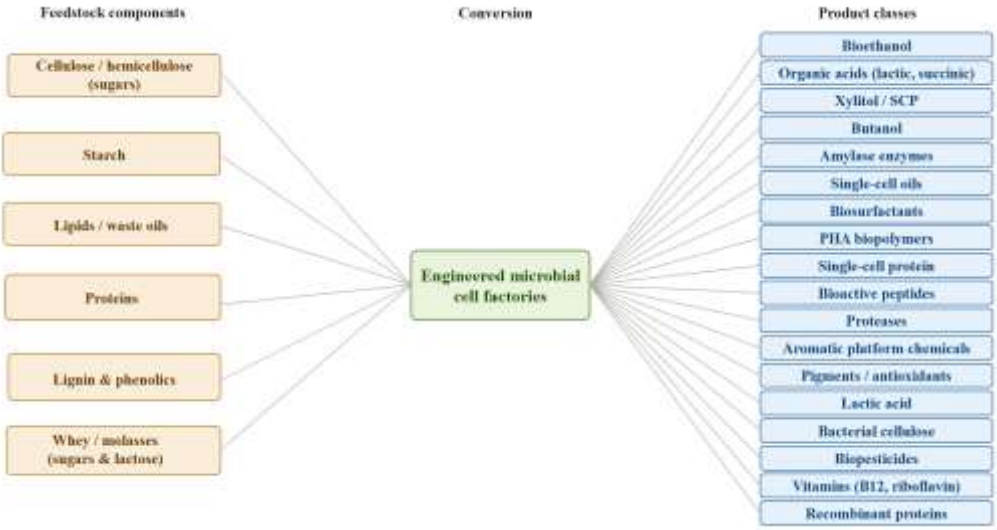


Fig. 2: Representative feedstock-to-product conversion pathways linking major residue components to microbial product classes.

3. FEEDSTOCK PREPARATION AND PRETREATMENT STRATEGIES

Milling, grinding, and other size reduction processes make more surfaces available for enzyme or microbial action and are generally the first type of pretreatment performed on solid lignocellulosic wastes; as a purely mechanical process, chemical free physical pretreatment does not create any inhibitory chemicals, although it is highly energy intensive. Acid and base pretreatments destroy the lignin-hemicellulose complex and make fermentable sugars quickly available, whereas solvent pretreatments (organosolv pretreatment) allow selective separation of lignin from the polysaccharides, but both types of pretreatment need to be neutralized and detoxified afterwards.[1,2,4]

Biological pretreatment using fungal cultures degrading lignin and cellulose or enzymatic hydrolysis with cellulase/hemicellulase enzymes mixture provides a more gentle approach without creation of many inhibitory chemicals; enzymatic hydrolysis was shown to be more compatible with microbial growth as compared to acid hydrolysis in case of using polyphenol-extracted cinnamon waste for carotenoid production. [2]

However, thermochemical pretreatment still results in formation of a number of microbe growth inhibitors along with fermentable sugars: furfural and 5-hydroxymethylfurfural (HMF) are formed from pentose and hexose dehydration respectively, phenols are formed due to lignin decomposition, while organic acids, like acetic acid, are formed due to decomposition of hemicellulose acetyl groups. All the above-listed chemicals work together to inhibit microbe growth and fermentation, and their concentrations depend on both feedstock type and pretreatment severity. [3]

The consequences of inhibitor formation depend on the interaction between the hydrolysate and the production organism. Inhibitory by-products reduce the performance of both enzymatic hydrolysis and microbial fermentation, so that growth, yield and productivity on a hydrolysate can be well below those on a defined sugar medium, and the same hydrolysate may be tolerated by one host and strongly inhibitory to another.[54,55] Inhibitor management therefore combines measures applied to the feedstock and the process, namely the choice of less severe pretreatment conditions, washing or conditioning of slurries and hydrolysates, and in-situ chemical detoxification with reducing agents, with measures applied to the organism, namely selection of tolerant hosts and adaptive laboratory evolution or genetic engineering of inhibitor tolerance (Section 5).[54,55] Because the

inhibitor profile depends on the feedstock and pretreatment severity, tolerance engineering and pretreatment design are best developed together rather than independently.

The compatibility of pretreated biomass with productive microbe growth can be achieved by means of detoxification, hydrolysis enzyme addition, proper nutrient balancing and adaption of production organism (Section 3.3 below). The evaluation of a particular pretreatment method is not to be conducted only on the basis of sugar extraction efficiency: the most appropriate pretreatment for a particular process is the one that combines maximal sugar yield, minimal amount of inhibitors for the selected production organism and economic and environmental proportionality to product value.[1,2,3]

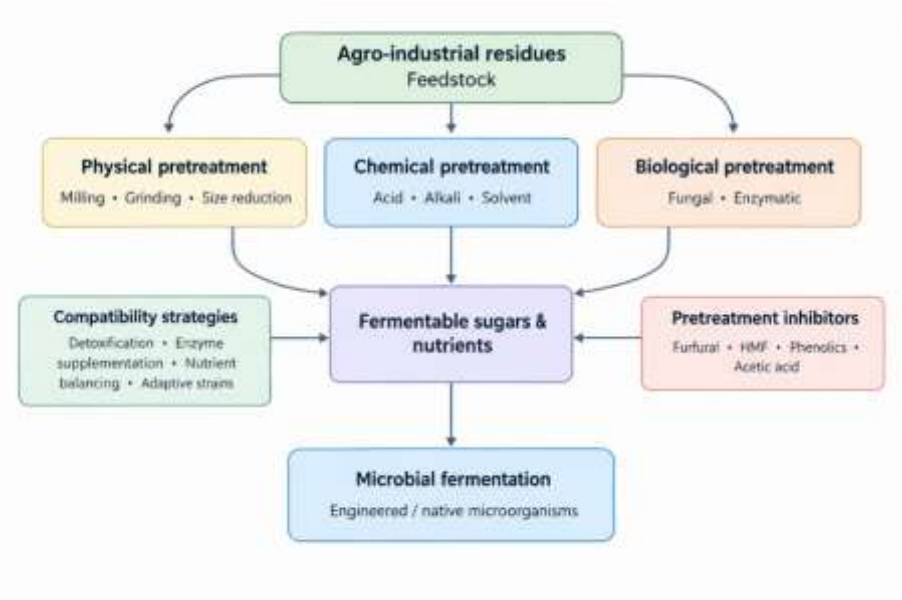


Fig. 3: Physical, chemical, and biological pretreatment routes, resulting inhibitor formation, and strategies used to restore feedstock-microbe compatibility.

4. MICROBIAL CELL FACTORIES: HOST SELECTION AND ENGINEERING STRATEGIES

The choice or construction of a microorganism suitable for waste biotransformation requires an assessment of the ability of that organism to utilize the available substrates and its capacity to tolerate feedstock-associated inhibitors. [4,5,12]

Escherichia coli is perhaps the best-studied engineered bacterium because of the thorough knowledge about its genetics and existing genetic methods, and has successfully produced organic acids, biofuels, and other chemical products from waste-derived sugars. [4] Bacillus strains are known for the secretion of extracellular enzymes and lipopeptide biosurfactants, whereas Corynebacterium glutamicum produces amino acids and organic acids from mixed sugars. [4]

Saccharomyces cerevisiae is currently the most commonly used industrial yeast strain for ethanol production and has been extensively engineered for pentose co-fermentation and tolerance to inhibitors for its use in lignocellulosic hydrolysates. [5,6] Yarrowia lipolytica is an indigenous oleaginous yeast capable of efficient utilization of lipid wastes like waste cooking oil and crude glycerol and has been engineered for co-production of lipase and single-cell protein from sugarcane molasses and for production of itaconic acid and sesquiterpene beta-farnesene from waste lipid sources. [7,8,9,10,11] Rhodosporidium toruloides has been adapted through adaptive laboratory evolution for tolerance to lignocellulosic hydrolysate inhibitors during accumulation of lipids and carotenoids. [12]

Aspergillus and Trichoderma species are the main producers of extracellular cellulases and hemicellulases and are widely used as both pretreatment agents and as producers of organic acids including citric acid, primarily by solid state fermentation technology.[48] Native organisms, which were initially discovered in waste and fermented food environments, typically exhibit better intrinsic resistance to waste streams, while engineered organisms enable broader substrate adaptation and non-native metabolic pathway implementation with the expense of more efforts and sometimes loss of genetic stability under industrial conditions.[4]

Table 2: Representative microbial hosts used for waste-to-value bioconversion

Host	Category	Representative waste substrate	Reported application
Escherichia coli	Bacterium	Lignocellulosic sugar hydrolysates	Organic acids, biofuels, specialty chemicals[4]
Bacillus subtilis	Bacterium	Agro-industrial waste, sludge	Lipopeptide biosurfactants, hydrolytic enzymes[4,44,48]
Corynebacterium glutamicum	Bacterium	Molasses, mixed sugars	Amino acids, organic acids[4]
Saccharomyces cerevisiae	Yeast	Lignocellulosic hydrolysate	Bioethanol; inhibitor-tolerant platform strains[5,6]
Yarrowia lipolytica	Yeast	Waste cooking oil, molasses, crude glycerol	Single-cell oil, lipase + SCP, itaconic acid, beta-farnesene[9,10,11]
Rhodosporidium toruloides	Yeast	Lignocellulosic hydrolysate	Microbial lipids, carotenoids[12]
Aspergillus niger	Filamentous fungus	Fruit pomace, starchy residues	Citric acid, amylases, cellulases [48]
Lactiplantibacillus plantarum	Lactic acid bacterium	Lignocellulosic hydrolysate	Lactic acid (inhibitor-tolerant evolved strains)[15]

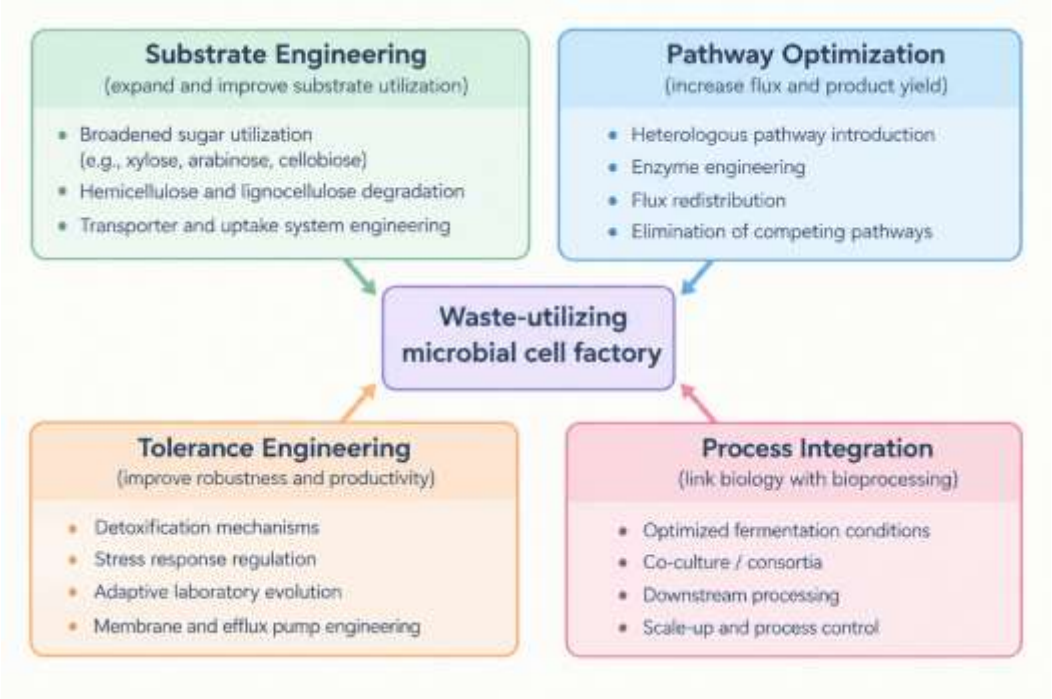


Fig. 4: Complementary engineering strategies applied to waste-utilizing microbial cell factories: substrate engineering, pathway optimization, tolerance engineering, and process integration

5.METABOLIC ENGINEERING AND SYNTHETIC BIOLOGY FOR EFFICIENT WASTE CONVERTION

Since lignocellulosic hydrolysates comprise a mixture of hexose and pentose sugars which industrially preferred hosts lack the ability to co-utilize effectively, substrate range engineering involving the engineering of pentose sugar transporters and

metabolic pathways along with relief from carbon catabolite repression has remained one of the consistent targets in strain development efforts, particularly for xylose fermenting S. cerevisiae. Having established substrate utilization, the next step involves balancing the heterologous pathway for the products with the host's metabolism using enzyme homology searches and metabolic flux redistributions based on flux balance analysis.[5,6,13,17,19]

Adaptive laboratory evolution (ALE) has proven very useful in providing inhibitor tolerance; gradual exposure to furfural and acetic acid has resulted in multi-inhibitor tolerant strains of S. cerevisiae, [13] while [14] chemical mutagenesis in combination with ALE under rice straw hydrolysate inhibitors has created inhibitor tolerant strains of a chassis organism. Similarly, furan tolerance and production of lactic acid have been increased in Lactiplantibacillus plantarum and ethanol productivity in Pichia kudriavzevii using ALE. [3,15]

Genomic sequencing of the evolved strains usually uncovers the mutations in transporters, transcriptional regulators, and aldehyde dehydrogenases which cause enhanced tolerance, while CRISPR-based approaches have been employed in order to speed up the evolution process directly; such as CRISPR-assisted evolution to obtain furfural tolerant strains of E. coli. [16]

The ability of synthetic biology techniques — promoter libraries, inducible genetic circuits, metabolite responsive genetic circuits and modular pathway assembly standards — to fine-tune heterologous gene expression is useful when optimal expression levels vary according to feedstock composition.[17] Genome editing tools that utilize CRISPR-Cas9 interference or activation systems have emerged as the standard methods of choice for targeted and genome-scale, multiplex strain engineering, as systems-level modeling tools are developed to facilitate the selection of appropriate targets for CRISPRi and CRISPRa programs. [18,19] Large genome-scale libraries obtained by multiplex or parallel genome editing approaches are increasingly employed for the identification of non-intuitive targets for strain improvements beyond the scope of serial engineering of individual genes. [20]

Profiling the genomes, transcriptomes, proteomes and metabolomes of parental strains compared to their improved variants helps in elucidating the underlying causes of phenotypic traits. As seen throughout the review, the combination of synthetic biology, multi-omics profiling and metabolic engineering constitutes the most promising methodological triad to help close the remaining gap between lab-scale fermentations of hydrolysates and industrially feasible waste-to-value processes.[17,18,19,20]

6.CONVERTION OF AGRO-INDUSTRIAL RESIDUE INTO HIGH-VALUE BIOPRODUCT

Bioethanol remains the largest-volume bioproduct derived from agro-industrial residues, produced principally by engineered, pentose-co-fermenting and inhibitor-tolerant S. cerevisiae strains from lignocellulosic and starchy feedstocks; butanol and other platform chemicals are produced through solventogenic Clostridium fermentations and, increasingly, engineered E. coli and yeast pathways operating on waste sugars.[4,5,6]

Polyhydroxyalkanoates (PHAs), microbial polyesters that can substitute petroleum-derived plastics, have been produced from diverse agro-industrial wastes including molasses, whey, cacao shells, and chickpea and bean residues, using wild-type isolates such as Bacillus tropicus, which accumulated 44.5% PHA of cell dry weight on domestic kitchen waste, [21,22] and halophilic and extremophilic hosts capable of tolerating high-salinity, complex waste streams. [23] Solid-state cultivation on starch- and chickpea-based agro-industrial waste, bioelectrochemical production strategies, and life-cycle-informed process design have further expanded the range of feasible PHA-generating waste-microbe combinations. [36,37,38,42,43,50]

Bacterial cellulose is a second major biomaterial target: optimized static and agitated cultivation, co-cultivation, stepwise nutrient feeding, and genetic engineering strategies have been described for producing bacterial cellulose from fruit peels, sugarcane bagasse, cereal straws, and corn stover, with applications spanning food packaging, biomedicine, and cosmetics. [24] Amylases, cellulases, proteases, and lipases produced via solid-state or submerged fermentation of agro-industrial residues serve both as process aids and as standalone commercial products, with Aspergillus and Bacillus species the dominant production hosts.[24,48]

Glycolipid biosurfactants, particularly rhamnolipids produced by Pseudomonas aeruginosa, and lipopeptide biosurfactants such as surfactin from Bacillus subtilis, have been produced from agro-industrial substrates including corn steep liquor, sugarcane molasses, bakery waste, and jackfruit waste, with combined-substrate strategies reported to improve titers. [25,26,27,35,40] Bacillus subtilis strains isolated from oil-contaminated sludge additionally produce biosurfactants with concurrent hydrocarbon-degrading activity. [44] Techno-economic and life-cycle assessments of rhamnolipid production identify carbon-source cost and

downstream purification as the dominant contributors to overall process cost relative to petrochemical surfactant production. [28,29,41]

Lactic acid, succinic acid, citric acid, and itaconic acid are among the most extensively studied waste-derived organic acids: lactic acid bacteria including inhibitor-evolved Lactiplantibacillus plantarum strains ferment lignocellulosic hydrolysates directly to lactic acid, while engineered Yarrowia lipolytica has been used to convert waste cooking oil into itaconic acid through subcellular (peroxisomal) pathway engineering. [10,15] Processed dairy whey similarly serves as a low-cost fermentable substrate for lactic acid production, and lignocellulosic feedstocks more broadly support microbial biorefining toward a wider range of organic acids beyond lactic and itaconic acid. [39,47]

Oleaginous yeasts, particularly Yarrowia lipolytica and Rhodosporidium toruloides, accumulate single-cell oils from lipidic and lignocellulosic wastes that can serve as biodiesel precursors, and pathway engineering has extended these platforms to non-lipid products such as the sesquiterpene beta-farnesene. [8,11]

Pigments, antioxidants, and antimicrobial secondary metabolites can also be recovered from microbial cultivation on residue-derived hydrolysates; enzymatically hydrolyzed cinnamon processing waste, obtained after polyphenol extraction, has for example been used as feedstock for microbial carotenoid production, illustrating sequential extraction of one high-value fraction followed by microbial valorization of the residual stream within the same biorefinery. [2]

Solid-state fermentation of lignocellulosic and other agro-industrial wastes by fungi and yeasts is widely used to generate protein-enriched biomass for animal feed; engineered Yarrowia lipolytica strains have additionally been used to co-produce feed-grade lipase together with single-cell protein biomass from sugarcane molasses, waste cooking oil, and crude glycerol, reaching reported single-cell protein titers above 150 g/L at pilot fermentation scale. [9,30,45,46 [

The reported conversion strategies differ in their level of technological development, with many studies demonstrated at laboratory scale and relatively fewer evaluated at pilot or industrial scale. Consequently, reported yields, titers and process improvements should be interpreted in relation to the scale and experimental conditions used in each study. The scale or process status of the selected examples is indicated in Table 3 where information is available.

Table 3: Selected waste feedstock to engineered-microorganism to bioproduct conversions with reported engineering strategy and outcome

Waste feedstock	Microorganism	Target product	Engineering strategy	Scale/Status	Reported outcome
Lignocellulosic hydrolysate (rice straw) *(crop residue)*	Saccharomyces cerevisiae (evolved)	Bioethanol / platform strain	EMS mutagenesis + adaptive laboratory evolution	Laboratory	Multi-inhibitor tolerance to furfural, acetic acid, phenol [14]
Sugarcane molasses / waste cooking oil / crude glycerol *(sugar/ starch and oilseed residues)*	Yarrowia lipolytica	Lipase + single-cell protein	Homologous lipase overexpression	Bench scale (10 L fermenter)	16,420 U/. mL lipase; 1512 g/L SCP (10 L scale) [9]
Waste cooking oil *(oilseed residue)*	Yarrowia lipolytica	Itaconic acid	Peroxisomal (subcellular) pathway engineering	Laboratory	Improved itaconic acid titer from lipid substrate [10]
Rye straw hydrolysatef *(crop residue)*	Yarrowia lipolytica	Single-cell oil	Xylose-pathway induction /	Laboratory	Improved lipid accumulation on xylose-rich hydrolysate.[7]

			genome modification		
Domestic kitchen waste / mixed fruit pulp *(fruit and vegetable residue)*	Bacillus tropicus	Polyhydroxyalkanoates	Native isolate screening + OFAT optimization	Laboratory	44.5% PHA of cell dry weight [21]
Corn steep liquor + sugarcane molasses *(sugar/ starch residue)*	Rhizobacterial isolate	Rhamnolipid biosurfactant	Mixed-substrate medium optimization	Laboratory	3.2 g/L rhamnolipid [27]
Lignocellulosic hydrolysate *(lignocellulosic crop residue)*	Lactiplantibacillus plantarum JGR2 (evolved)	Lactic acid	Adaptive laboratory evolution	Laboratory	Enhanced furan tolerance and lactic acid productivity [15]
Rice straw / corn stover / fruit peels *(crop and fruit/ vegetable residues)*	Komagataeibacter spp.	Bacterial cellulose	Co-cultivation, stepwise feeding, strain engineering	Mixed (review); mostly laboratory	Enhanced furan tolerance and lactic acid productivity.[24]

Note: Scale/Status refers to the scale described in the cited study. Laboratory denotes flask or bench-scale experiments; none of the listed conversions is claimed here as an industrial or commercial process. Residue classes in the first column follow Table 1.

7.PROCESS ENGINEERING AND BIOREFINERY

Submerged fermentation is preferred for liquid or slurry feedstocks and offers precise control of dissolved oxygen, pH, and temperature, while solid-state fermentation is well matched to fibrous, low-moisture residues and is widely used for enzyme, organic-acid, and single-cell-protein production.[34,49] Batch and fed-batch modes dominate current industrial practice, with fed-batch feeding used to manage inhibitor exposure and substrate-mediated repression. [34,49]

Division of metabolic labor across two or more microorganisms -- for example, a syntrophic partnership of Bacillus subtilis and Clostridium acetobutylicum for biohydrogen production from agro-food waste -- can improve overall substrate utilization and product yield beyond that of a monoculture, at the cost of more complex process control. [31]

Rather than targeting a single product, integrated biorefineries recover multiple products in sequence from the same feedstock stream, improving overall carbon and economic utilization of the incoming residue. Product recovery and purification frequently represent the largest share of total production cost for waste-derived bioproducts, particularly for biosurfactants and organic acids, and standard fermentation parameters (pH, temperature, nutrient balance, aeration, duration) require re-optimization for each waste feedstock since real residues differ systematically from defined laboratory media. Translation from laboratory to pilot and industrial scale introduces additional variables, including batch-to-batch feedstock consistency and mixing/mass-transfer limitations in large bioreactors. [1,28,29]

Downstream processing deserves particular attention because the product concentration reached in the broth largely determines the recovery effort. Dilute broths, cells, residual substrate and impurities carried over from real residue streams complicate separation, and purification has been estimated to account for roughly 20-40% of the total cost of biochemical production processes, with the exact proportion depending on the product and the broth concentration.[56,57] The recovery route (for example cell removal, extraction, adsorption, membrane separation, crystallization or distillation) must be matched to the product class, its concentration and the required purity, and recovery efficiency, energy demand and water use should be reported together with titer, yield and productivity. Process-integrated and in-situ product removal, heat integration, and recycling of microbial biomass and water have been shown to lower energy demand, cost and fresh-water use in the recovery of volatile products from fermentation broths.[56]

Scale-up of industrial microbial processes is a high-stakes step that can require time and investment exceeding those of laboratory development, and it should be planned from the start of strain and process development, with piloting as an integral stage.[58] Several factors that are negligible in shake flasks become controlling at larger scale: mixing time and the resulting gradients in substrate, pH and dissolved oxygen; oxygen transfer, since the oxygen demand of dense aerobic cultures can exceed the transfer capacity of large vessels; heat transfer, since metabolic heat and agitation power must be removed; and rheology, since fibrous or high-solids residue slurries, filamentous fungi and polymer-producing cultures raise broth viscosity and impair mixing and mass transfer. Cells circulating through such gradients experience fluctuating conditions that can lower yield and productivity, and scale-down simulators, controlled feeding strategies, dissolved oxygen and pH control, and online sensing are used to anticipate these effects.[58,59] Results obtained on laboratory hydrolysates should therefore be regarded as indicative until they are confirmed at pilot and demonstration scale with real and variable feedstock.

The comparison and transfer of results between studies are currently limited by the absence of common standards for describing feedstocks and processes. Studies on residues differ in residue origin, particle size, moisture, pretreatment severity, hydrolysate composition, nutrient supplementation, inoculum, and fermentation mode and duration, so that reported titers and yields cannot always be compared directly. Consistent characterization of each feedstock lot with standardized compositional methods,[52] reporting of pretreatment conditions and inhibitor concentrations in the hydrolysate,[54] and the use of defined fermentation conditions and a reference medium in each study would improve reproducibility between batches, laboratories and scales. Where possible, feedstock specifications and quality control at the supply stage should be agreed in advance to limit batch-to-batch variability.[51,53]

8.CIRCULAR BIOECONOMY AND SUSTAINABILITY ASSESSMENT

Circular bioeconomy models seek to close material loops by recovering value from residue streams that would otherwise be discarded and, where possible, recycling process by-products back into the production system as nutrients or energy inputs. Diverting agro-industrial residues from landfilling or open burning toward microbial conversion reduces uncontrolled methane and particulate emissions, and displacing petroleum-derived plastics, surfactants, and chemicals with microbially produced equivalents can reduce fossil-resource dependence and net greenhouse gas emissions under favorable process conditions.[1,32]

Life cycle assessment (LCA) studies of waste-derived bioproducts, including biopolymers and biosurfactants, quantify environmental impact categories such as carbon footprint and energy and water consumption across the production chain, and are increasingly used alongside techno-economic analysis to identify disproportionately burdensome process stages. [32]

Techno-economic assessments of rhamnolipid production at industrial bioreactor scale have benchmarked biosurfactant production economics directly against petrochemical surfactant manufacture, identifying feedstock cost, fermentation productivity, and downstream processing as the dominant levers available to improve process economics. [28]

Locating bioconversion facilities at or near the point of residue generation reduces transport cost and feedstock degradation prior to processing and can enable industrial symbiosis arrangements. A recurring conclusion across the sustainability literature is that biological feasibility and commercial or environmental feasibility must be assessed separately: a fermentation that performs well on a laboratory-prepared hydrolysate does not, by itself, establish that the corresponding process is economically viable or environmentally favorable once feedstock logistics, pretreatment energy demand, and downstream recovery are included in the analysis. [28,32]

Energy integration is a further design dimension of the biorefinery concept. Residual streams such as lignin-rich solids, spent biomass and biogas from effluent treatment can supply process heat and power within the plant, and renewable electricity, for example from solar photovoltaics, can be used to drive the process. In a techno-economic case study of an electrified lignocellulose biorefinery step, a configuration combining photovoltaic electricity with grid supply offered a better trade-off between cost and emissions than islanded photovoltaic operation, which was limited by intermittency and scaling, while the carbon intensity of the grid strongly influenced the emission benefit.[60] The benefit of renewable energy integration should therefore be quantified for each process rather than assumed.

Water use and wastewater management are equally important. Biorefineries require process water for pretreatment, washing, media preparation and cooling, and they generate effluents with a high organic load; for lignocellulosic ethanol production, bioconversion wastewater was reported to carry up to 260 kg of biological oxygen demand per tonne of feedstock, with the inorganic load increased by pretreatment and pH adjustment, which supports integrating wastewater treatment into process

design.[61] Reducing freshwater demand through recycling and reuse of process streams and, where feasible, the use of non-potable water such as seawater has been proposed to lower both the water footprint and the process cost.[56,62] Water consumption, recycling rates and effluent quality should be included in the sustainability assessment alongside carbon footprint and energy demand.

Independent assessment is needed before industrial feasibility is claimed. In-depth technical, economic and environmental assessment is considered essential before large-scale deployment of a biorefinery, regardless of its technology readiness level,[63] and such analyses depend on assumptions and are subject to uncertainty. Claims of industrial feasibility should therefore be supported by independent techno-economic analysis that uses realistic feedstock, process, scale, energy, logistics and downstream-processing assumptions, including residue collection and transport, pretreatment, enzyme and nutrient costs, utilities, product recovery and wastewater treatment, together with sensitivity or uncertainty analysis. Likewise, environmental claims should be validated by independent, full-system life cycle assessment with clearly defined system boundaries and allocation of impacts among co-products, covering feedstock transport, pretreatment, water, energy and downstream processing, and ideally combined with the techno-economic analysis in a consistent framework.[28,32,63]

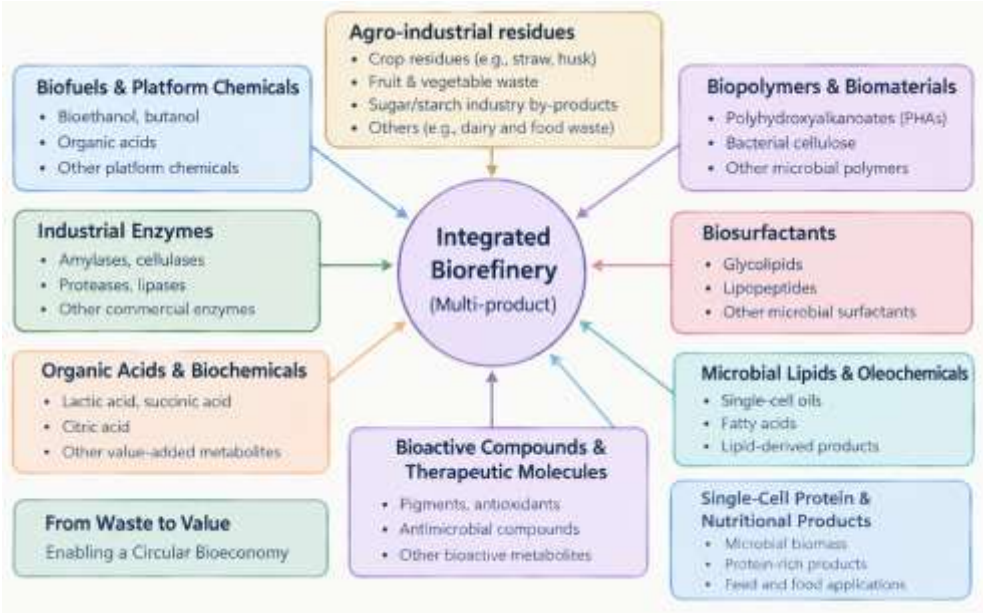


Fig. 5: Integrated circular biorefinery model showing multiple product streams recovered from a single agro-industrial residue input and reuse of residual process streams.

9. CHALLENGES, RESEARCH GAPS AND FUTURE PERSPECTIVES

Several interlinked challenges continue to limit industrial translation of waste-to-value microbial biotechnology: feedstock heterogeneity across season, variety, and geography; incomplete co-utilization of mixed sugars and residual polymeric fractions; persistent microbial inhibition by pretreatment-derived furfural, HMF, phenolics, and organic acids even in engineered or evolved tolerant strains; product yields on real waste hydrolysates that fall short of those obtained on defined synthetic media; loss of heterologous pathways or evolved phenotypes over extended industrial cultivation in the absence of selective pressure; mass-transfer, mixing, and feedstock-consistency challenges at pilot and industrial scale; high downstream recovery and purification costs, particularly for biosurfactants and organic acids; jurisdiction-dependent regulatory and biosafety considerations for engineered production strains; and a general scarcity of studies combining techno-economic assessment and life-cycle assessment within a single waste-to-value process evaluation. [1,13,15,16,20,28,32,34]

Regulatory and biosafety requirements for engineered production strains also deserve explicit consideration, because they depend on the organism, the genetic modification and the intended use, and they can affect process design, product approval and market access. Industrial fermentations with engineered strains are generally carried out in closed systems, in which physical containment, inactivation of waste streams and monitoring are the main safeguards against release;[64,65] biological measures such as auxotrophy, kill switches and genetic recoding are being developed to supplement them, and horizontal transfer of genetic

material is a recognized concern.[64] Regulatory frameworks distinguish contained use from deliberate environmental release. In the European Union, contained use of genetically modified micro-organisms is governed by Directive 2009/41/EC, which requires risk assessment and containment measures proportionate to the risk;[66] in India, the 1989 Rules under the Environment (Protection) Act, 1986 regulate the manufacture, use, import, export and storage of genetically engineered organisms and cells;[67] and in the United States the Environmental Protection Agency regulates commercial use of intergeneric microorganisms under the Toxic Substances Control Act through a Microbial Commercial Activity Notice, with exemptions for well-characterized hosts subject to containment conditions.[68] Products intended for food or feed may in addition require product-level approval. Regulatory status should therefore be considered at the strain-design stage, favoring well-characterized host organisms, genomically integrated and marker-free constructs, and process designs that allow verified containment and inactivation of effluents.

Machine learning methods are increasingly applied to predict effective CRISPR guide RNA designs, optimize enzyme selection for heterologous pathways, and link genotype to complex phenotype, complementing experimental strain engineering and offering a route to accelerate design cycles for waste-adapted production strains. [18] Constraint-based genome-scale metabolic models and algorithms such as OptKnock and its successors are used to predict gene deletion, insertion, and medium-modification strategies that couple growth to product formation, including for multi-strain co-culture systems relevant to waste bioconversion. [19,33]

Integration of real-time process sensors with predictive process models, dynamic genetic circuits that sense and respond to metabolite concentrations, and combined multi-omics/synthetic-biology design pipelines are together expected to shorten the design-build-test-learn cycle for strains and processes intended to operate on complex, variable waste feedstocks. Translating these laboratory advances into industrial practice will nonetheless require sustained parallel investment in strain robustness, feedstock logistics, and integrated techno-economic and life-cycle evaluation, so that scale-up decisions are guided by demonstrated commercial and environmental viability rather than laboratory titer alone. [18,19,20,32,33]

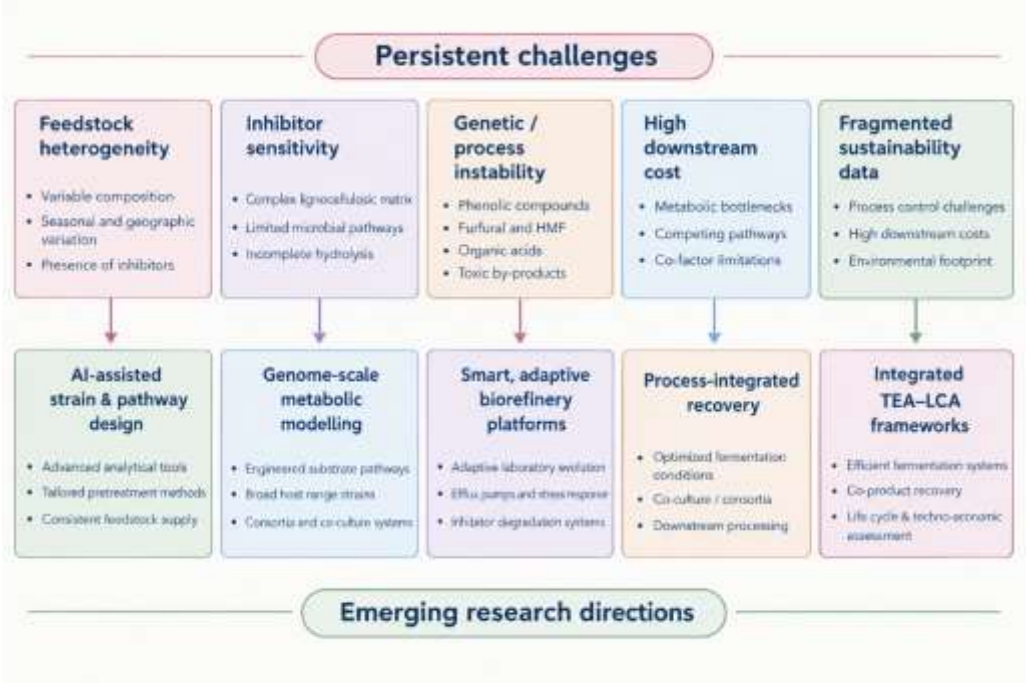


Fig. 6: Persistent challenges in waste-to-value microbial biotechnology mapped to corresponding emerging research directions

Table 4: Principal challenges, underlying causes, and emerging research opportunities in waste-to-value microbial biotechnology

Challenge	Underlying cause	Emerging research opportunity
Feedstock heterogeneity	Seasonal, varietal, and geographic variation in residue composition	Real-time feedstock characterization; adaptive process control.[1]
Inhibitor sensitivity	Furfural, HMF, phenolics, organic acids from pretreatment	Adaptive laboratory evolution; CRISPR-accelerated tolerance engineering .[13,15,16]
Low substrate utilization	Incomplete co-utilization of mixed sugars and polymers	Expanded substrate-range engineering; enzyme cocktail optimization [19,33.]
Strain instability	Loss of heterologous pathway or evolved phenotype under industrial cultivation	Genome-integrated, growth-coupled pathway design .[6,20]
High downstream cost	Complex separations for organic acids, biosurfactants, biopolymers	Process-integrated recovery; in-situ product removal [28,29]
Fragmented sustainability data	Techno-economic and life-cycle assessments rarely combined	Standardized integrated TEA-LCA frameworks for waste bioprocesses [32]

10.CONCLUSION

Agro-industrial residues represent an abundant and diverse source of renewable material which can potentially provide a basis for microbial production of biofuels, biopolymers, enzymes, biosurfactants, organic acids, lipids, bioactive molecules, and single-cell protein. The realization of this potential involves treating the microbial cells as engineerable organisms whose substrate spectrum, biosynthetic pathways, and tolerance to stress can be designed according to the characteristics of the specific feedstock. The advances in metabolic engineering, synthetic biology, adaptive laboratory evolution, and multi-omics-based strain optimization have together increased the number of feasible feedstock-microbe-product combinations that could be run at economically viable productivity levels. Process integration and biorefinery approaches are starting to enable capturing multiple value streams from one type of the feedstock. The heterogeneity of the feedstock, incomplete utilization of substrates, recovery cost of products, and lack of integrated techno-economic and life-cycle assessments are the main obstacles in moving from lab-scale demonstration to commercial implementation of such processes. Resolving these challenges requires further collaboration of strain engineering with process engineering and sustainability assessments through novel computational and AI-based design approaches. [1,4,17,18,19,32]

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Lorem ipsum dolor sit amet, consectetur adipiscing elit. The authors acknowledge the technical assistance provided by the Department of Natural Resources.

AUTHOR CONTRIBUTIONS

Lorem A. Ipsum: Conceptualization, Investigation.

Dolor B. Sit: Methodology, Laboratory Analysis.

Amet C. Consectetur: Data Curation, Formal Analysis.

Adipiscing D. Elit: Supervision, Writing—Review & Editing.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ETHICS STATEMENT

DATA AVAILABILITY STATEMENT

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