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Review

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Organic wastes to next-generation bioplastics through intelligent biomanufacturing of polyhydroxyalkanoates

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Organic waste generation continues to pose major environmental challenges, including greenhouse gas emissions, soil and water contamination, and resource depletion. Here, we highlight how intelligent biomanufacturing integrating engineered microbes, waste-derived feedstocks, green extraction techniques, and AI-driven optimisation can convert diverse organic residues into high-value PHA bioplastics. This approach offers sustainable production pathways, eco-friendly recovery strategies, and data-driven process optimisation within a circular bioeconomy framework to support scalable, low-impact bioplastic manufacture.

Bioplastics have emerged as a cornerstone in the transition toward sustainable materials, offering viable alternatives to conventional petroleum-based polymers. Derived from renewable biological feedstocks and often designed to be biodegradable, these materials aim to minimise both plastic waste and fossil fuel use[1]. Among the diverse classes of bioplastics, polyhydroxyalkanoates (PHAs) have attracted particular attention[2]. PHA production is a growing area of industrial biotechnology, making these biopolymers important for sustainable innovation, with current global production on the order of ~3–5 × 10^4 tonnes per year and an estimated market value of ~USD 0.2–0.3 billion[3]. PHAs represent a new generation of bioplastics that bridge the gap between environmental sustainability and functional performance. Beyond their biodegradability, PHAs also offer distinct advantages over many other biopolymers, including marine degradability and high tensile strength comparable to some petroleum-based plastics[2]. PHAs exist in various forms. The simplest type is poly(3-hydroxybutyrate) (PHB), which is highly crystalline and strong but also brittle. Copolymers such as poly(3-hydroxybutyrate-co-3-hydroxyvalerate) (PHBV) include 3-hydroxyvalerate (3HV) units, which reduce crystallinity and lower the melting temperature. For example, PHBV containing about 10 mol% 3HV melts at around 148–168 °C and is much more flexible than PHB. This ability to adjust PHA composition allows their mechanical and thermal properties to be tailored for different applications[4].

Recent studies demonstrate the growing role of artificial intelligence in PHA bioprocess optimisation. For example, response surface methodology combined with genetic algorithm-optimised artificial neural networks has been used to co-optimise nutrient concentrations and incubation time for *Cupriavidus necator*, achieving more accurate prediction of PHA yield than conventional polynomial models[5]. At the materials and processing level, artificial neural networks have been applied to optimise additive manufacturing parameters of PHA blends, enabling accurate prediction of mechanical performance and identification of optimal printing conditions[6]. Together, these studies illustrate how data-driven approaches can improve both bioprocess efficiency and material functionality in PHA-based systems and broadened their potential application across diverse sectors, including food packaging, textiles, agriculture, automotive, electronics, and medicine[7]. On the other hand, PHAs can be applied either as pure polymers or copolymerized with other substances, allowing their properties to be modified for targeted uses. Recently, materials such as starch/PHA blends, PLA/PHA nanocomposites formulated with various loadings of graphene oxide and 2,2,6,6-Tetramethylpiperidine-1-oxyl (TEMPO)–oxidized cellulose, and blends of PHA with cellulose derivatives have all been successfully explored for food packaging uses[8–12]. In addition, Researchers are engineering or selecting bacteria that both accumulate PHAs and produce valuable co-metabolites. For example, *Paracoccus* spp. well-known for astaxanthin (a high-value carotenoid), have been shown to co-produce PHAs (including PHBV) and astaxanthin when grown on waste-derived sugars[13].

A bibliometric analysis using the Web of Science (WOS) database was carried out to explore research trends in polyhydroxyalkanoates (PHAs) (Fig. 1). Figure 1a shows a keyword co-occurrence network in which PHAs appear as the main and most influential topic, strongly connected to

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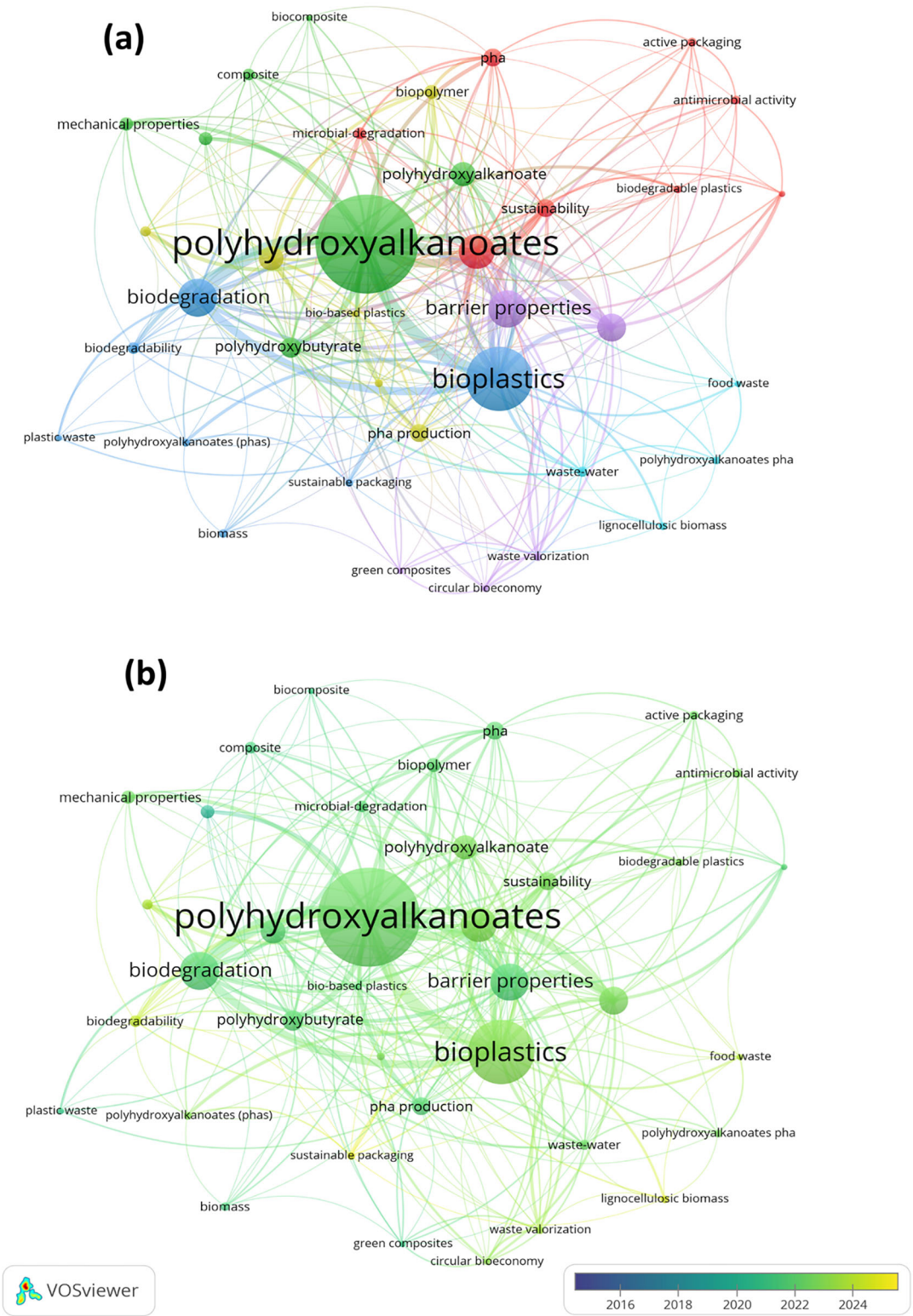

Fig. 1 | Literature trends: Bibliometric mapping of keyword co-occurrence of publications related to polyhydroxyalkanoates (PHAs). a Literature trends: Bibliometric mapping of keyword co-occurrence in published studies. **a** The size of each node represents how frequently that keyword appears, while the connecting lines indicate keywords that occur together in the same articles. A shorter distance between two nodes reflects a higher frequency of their co-occurrence. **b** Keyword co-occurrence network of publications related to polyhydroxyalkanoates (PHAs) generated using VOSviewer based on data from the Web of Science database (2015–2025). Node size represents keyword frequency, while link thickness indicates the strength of co-occurrence. The color gradient from blue to yellow denotes the average publication year, showing a research shift toward recent themes such as sustainability, bioplastics, and food packaging.

bioplastics, biodegradation, barrier properties, and mechanical performance. Broader terms such as biopolymers and biodegradable polymers mainly appear as application-related extensions of PHA research, highlighting the central role of PHAs in the sustainable polymer field. Figure 1b presents a temporal overlay analysis from 2015 to 2025, showing how research priorities have changed over time. While PHA-related topics remain central throughout the period, recent studies increasingly focus on practical and sustainability-driven applications, including food packaging, waste valorization, and the circular bioeconomy. Overall, the analysis shows a stable PHA-focused research core with growing emphasis on sustainable and high-performance PHA-based materials for packaging applications.

This review presents a concise overview of recent advances in PHA-based bio-composites, emphasizing their development, processing, use of artificial intelligence in production optimization, and applications in sustainable packaging. It discusses PHA synthesis, microbial production, and green extraction methods, along with the incorporation of eco-friendly nanomaterials such as cellulose, lignin, chitosan, sludge, microalgae, and biochar to enhance performance and biodegradability. The review highlights green fabrication techniques, progress in intelligent and compostable packaging, and industrial relevance. In addition, this review is organised around the following roadmap: Waste feedstocks → PHA biosynthesis → Green extraction technologies → AI / Industry 4.0–5.0 optimisation → Intelligent end-of-life and degradation. Intelligent biomanufacturing is presented as a unifying framework that links all stages of PHA development through data-driven decision-making and lifecycle feedback. Rather than focusing only on fermentation optimisation, it integrates feedstock selection, downstream processing, polymer property prediction, and degradation-aware material design. In contrast to previous PHA reviews, which typically address microbial production, material properties, or biodegradation as separate topics, this review treats these elements as an interconnected, intelligent value chain. The novelty of this review lies in viewing PHA development as a connected, intelligent value chain rather than a set of isolated technological advances. By combining technological, environmental, and industrial perspectives across the full lifecycle from waste-based feedstocks and green extraction to AI-supported scale-up and controlled biodegradation, this review highlights practical strategies to address challenges in cost, scalability, and feedstock availability, and to advance truly circular and sustainable plastic systems.

The green alchemy of plastics: from waste to PHA

Biopolymers have emerged as sustainable alternatives to conventional plastics in food packaging, addressing issues of non-biodegradability and plastic pollution. Derived from renewable resources and agro-food waste, they offer both environmental and functional advantages[14,15]. PHA-based green composites have attracted significant attention in recent years owing to their excellent biodegradability and biocompatibility. These eco-friendly PHA composites serve as promising alternatives to conventional non-biodegradable materials that pose environmental concerns[16]. Currently, industrial PHA production depends largely on fermenting sugars and oils sourced from edible crops like corn, sugarcane, and vegetable oils. Because these food-based materials can represent more than half of the overall production cost, shifting toward inexpensive biomass is an important step forward. Residues from agriculture and forestry, food-processing waste, and crops offer a cost-effective alternative carbon source for PHA synthesis[17]. Table 1 compares recent major organic waste feedstocks and effective studied microbial cultures for PHA production. Lignocellulosic biomass primarily consists of carbohydrate-rich components like cellulose and hemicellulose, and lignin.

Lignocellulose is chemically made up of three main components: cellulose, which accounts for 40–80%, hemicellulose at 10–40%, and lignin, ranging from 5% to 25%[18]. Beyond traditional lignocellulosic sources, food waste from agriculture, food industries, restaurants, and homes also represents a promising carbon source for PHA generation[17]. However, because lignocellulosic biomass is highly resistant to breakdown, microorganisms cannot use it directly. As a result, it must undergo pretreatment to

Table 1 | Comparative performance of waste-derived feedstocks and various microbial cultures used for PHA production

Feedstock	Pretreatment	PHA Yield (% of CDW)	Microbial Culture	Ref.
Lignocellulose	Acid or enzymatic hydrolysis of cellulose/hemicellulose; Detoxification of inhibitors required.	PHA accumulation: ~50–70% (e.g. 54% from bagasse, 59% on maple hydrolysate)	*Cupriavidus necator*, *Burkholderia sacchari*, *Bacillus sp. Rhodopseudomonas palustris*	17
Lignocellulosic biomass (Corn straw)	Acid-pretreatment and enzymatic digestion of corn straw.	PHA accumulation: 3.98 g/L (*P. putida*, glucose + octanoate); 3.38 g/L (*E. coli*, xylose)	*Pseudomonas putida*, *Escherichia coli*	18
Sugarcane bagasse	Air-drying, cutting/milling, oven drying	High PHB yield (6.11 g/L in 20 h) achieved with optimized SCB hydrolysate.	*Bacillus megaterium*	19
Starch-rich wastes (Cassava Peel Starch)	Gelatinization/acid or enzymatic hydrolysis of starch into sugars.	~85–90% (e.g. 85.1–89.0% PHA content from hydrolyzed cassava peel starch.	*C. necator*	20
Lipid-rich waste (Saturated fatty acids (SFAs))	Minimal pretreatment (filtering; sometimes lipase/hydrolysis).	~70–75% (e.g. ~75% yield on C12–C14 fatty acids	*C. necator*	21
Waste-derived VFAs from food waste and primary sludge	Anaerobic fermentation of food waste and primary sludge to produce VFAs	*C. necator* accumulated 77.54 ± 5.67% of CDW), whereas Burkholderia cepacia reached 54.9 ± 3.66% of CDW.	*C.necator*, Burkholderia cepacia	22
Algal biomass (Algal biodiesel waste)	Direct use of glycerol-rich algal biodiesel waste residues	PHA accumulation reached 0.24 g L^{-1} (35% DCW), demonstrating efficient PHA production from waste biomass.	*Halophilic microbes, including Halomonas spp., H. daqingensis, and H. ventosae*	23
Algal biomass (Defatted *Chlorella* biomass)	Acid pretreatment to extract reducing sugars.	PHA accumulation: 29.7–75.4% DCW; highest in *C. necator* (7.51 ± 0.20 g L^{-1}, 75.4% DCW).	*B. megaterium*, *C. necator*, *and Haloferax mediterranei*	24
Wastewater (Yeast Industry)	Pretreating the sludge with heat and distilling the wastewater	PHA accumulation: 17% DCW; yield 1.2 g L^{-1}, using distilled wastewater.	*Paracoccus alcalophilus and Azoarcus sp.*	25
Waste sludge	Anaerobic digestion to produce volatile fatty acids (VFAs)	PHA accumulation: ~20–30% (e.g. ~30 g PHA /100 g sludge biomass.	Mixed microbial cultures	26

release fermentable sugars, adding complexity and requiring more advanced processing steps for its use in PHA production[19,20]. To address these challenges, the biorefinery concept has been proposed, in which lignocellulosic biomass is broken down and converted into multiple value-added products such as biofuels, chemicals, and biopolymers, including PHAs within an integrated processing framework, thereby improving resource efficiency and economic viability[21]. However, only a few microbial strains are able to metabolize C5 sugars and accumulate PHAs; if they do, conversion efficiencies have been low[22]. For example, Kingsly et al. demonstrate the effective production of polyhydroxyalkanoates (PHAs) using sugarcane molasses as a low-cost carbon source by a wild strain of *Enterobacter cloacae*. Under optimized conditions, the strain achieved a PHA yield of up to 4.98 g/L, corresponding to 56% of cell dry weight, highlighting its strong metabolic capability and potential for cost-effective and sustainable PHA production[23]. In addition, Barrameda et al. addressed a key challenge in PHA production from lignocellulosic biomass by developing and optimizing pretreatment strategies for sugarcane bagasse. Sequential steam explosion–dilute H_2SO_4 pretreatment significantly improved the release of fermentable sugars, achieving an 85.93% yield, compared with lower yields from steam explosion alone. The resulting hydrolysates were successfully converted into polyhydroxybutyrate (PHB) through bacterial fermentation, demonstrating that pretreated lignocellulosic residues can serve as an effective, low-cost substrate for sustainable PHA production[24].

Recent studies highlight that various agricultural and agro-industrial wastes can serve as effective substrates for PHA production, though their performance differs depending on composition and processing needs. Wheat straw hydrolysates produced through mild pretreatment can support moderate PHA formation with minimal additional inputs, making them a low-cost option despite generally lower yields[25,26]). Sugarcane bagasse offers similar potential but often requires more intensive pretreatment, which can introduce inhibitory compounds and reduce overall efficiency[27]. In contrast, nutrient-rich liquid wastes such as distilled wine lees are more easily utilized by microorganisms, especially extremophiles, and tend to support higher PHA productivity with fewer processing hurdles[28]. These comparisons show that while lignocellulosic materials are abundant and sustainable, liquid waste streams often offer greater accessibility and higher PHA yields.

Starch-rich waste streams offer a natural, renewable, and biodegradable polymer source that is widely available. Their low cost and abundance make waste-derived starch an attractive and economical raw material for developing new biopolymers[29]. Starch-rich residues from crops such as cassava, potato, wheat, and rice have been widely explored as carbon sources for PHA production. Cassava starch hydrolysates have supported good microbial growth and moderate PHB accumulation in *Cupriavidus* strains, demonstrating their suitability as accessible carbohydrate substrates. Potato processing residues have shown even stronger potential, with several *C. necator* strains achieving high biomass formation and notable polymer accumulation, indicating that potato waste tends to yield more efficient PHA conversion than cassava[30]. Wheat starch hydrolysates have also been used successfully, enabling *Bacillus* species to synthesize copolymers like Poly(3-hydroxybutyrate-co-3-hydroxyvalerate) (PHBV) directly from the waste without additional nutrient enrichment[31]. Rice-based residues, including rice husks and rice hydrolysates, have produced variable but promising PHA yields depending on the microbial strain, cultivation method, and supplementation. In optimized conditions, rice-derived substrates have supported higher polymer productivity than most other starch residues[32]. Overall, while all starch-rich wastes can be converted into PHAs, potato and rice residues generally lead to higher polymer accumulation, whereas cassava and wheat wastes offer simpler, low-cost processing routes with moderate yields.

Another notable category of waste-based substrates for PHA production is lipid-rich residues, particularly waste and used cooking oils. These oils provide a cheap and sustainable carbon source due to their high content of fatty acids, typically ranging from C12 to C20, that are easily converted by many PHA-producing microorganisms[33]. Multiple investigations have consistently found that waste cooking oil can perform better than fresh oil as a raw material for PHA production, likely because it is a mixture with high free fatty acid and partially degraded fatty acids that are more readily utilized by many PHA-producing bacteria[34]. Studies using *Pseudomonas* species have further confirmed that waste cooking oil can act as the sole carbon source while still achieving high levels of medium-chain-length PHA[35]. Despite these advantages, challenges remain: the low solubility of waste oils in water can limit substrate availability during later fermentation stages, especially when cell density increases. More recent work exploring bacterial strains isolated from environments such as activated sludge and industrial wastewaters highlights the potential for identifying robust microbes naturally adapted to oily waste streams, offering new opportunities to improve PHA production from lipid-rich residues[31].

Managing and reusing wastewater from municipal and industrial sources remains a persistent global challenge. Each year, wastewater treatment plants generate an estimated 80–90 million tons of waste-activated sludge (dry weight) worldwide[36]. Peng et al[37]. introduced a circular strategy for managing waste-activated sludge by integrating PHA production with biochar recycling. In this system, after PHA recovery, the remaining sludge was converted into biochar via pyrolysis and then reused as a catalyst during anaerobic digestion. Compared with a conventional biochar-free control system, the addition of biochar enhanced electron transfer and enriched PHA-accumulating microorganisms. As a result, PHA yield increased by more than 80%, reaching over 66% of the dry sludge mass. Another study showed that macroalgae can serve as both a sugar source and a biochar precursor for efficient PHA production. *Eucheuma spinosum*-derived biochar effectively removed fermentation inhibitors from algal hydrolysate, enabling *Halomonas* sp. YLGW01 to grow under unsterile, saline conditions and achieve much higher PHB yields than with untreated hydrolysate[38]. Microalgae also offer a sustainable and efficient way to make PHA bioplastics. These organisms naturally synthesize and accumulate PHA as internal carbon and energy reserves, positioning them as a cost-effective and environmentally sustainable platform for PHA production. Microalgae and cyanobacteria, including *Synechococcus*, *Scenedesmus* spp., *Dunaliella tertiolecta*, *Arthrospira platensis*, and *Chlorella vulgaris*, can accumulate PHAs within their cells, particularly under nutrient-limited conditions such as nitrogen or phosphorus deficiency. Among these organisms, *Synechococcus* and *Arthrospira* are cyanobacteria, while *Scenedesmus*, *Dunaliella*, and *Chlorella* are green microalgae[39]. The main achievement of the study by Roja et al.[40] was identifying *Lyngbya valderiana* and *Chlorella sp.* as promising microalgal strains for efficient PHA production, owing to their faster growth rates compared to *Odontella salina* and *Synechococcus elongatus*, which enhances their economic potential as bioplastic sources. Additionally, extracted PHAs had good stability below 260 °C, with *L. valderiana* producing the most thermally stable polymer, highlighting its suitability for industrial applications. Beyond wastewater-derived feedstocks, biochar has also emerged as a valuable tool for improving both PHA production and the performance of PHA-based materials. Biochar is a carbon-rich porous material typically produced by pyrolyzing waste or renewable biomass at high temperatures (approximately 300–900 °C) under oxygen-limited conditions. Its properties can be improved by activation either physically (using steam or CO_2) or chemically (using acids or alkalis) to increase surface area and functional properties. Producing biochar from biomass residues supports a circular economy by transforming organic waste into a valuable resource, sequestering carbon, and reducing the overall carbon footprint of bioplastic production systems[41]. Studies using biochar produced from agricultural residues have shown that even small additions of biochar can significantly enhance the mechanical strength, stiffness, and overall printability of PHA composites, particularly in applications such as 3D printing[42]. Biochar can also play an important upstream role in PHA bioprocessing. When used to treat biomass hydrolysates, biochar effectively removes inhibitory compounds generated during pretreatment, allowing microorganisms to grow more efficiently and synthesize substantially higher amounts of PHA compared with untreated substrates[38]. These findings show that biochar can both

strengthen PHA materials and help increase PHA production, making it a useful and sustainable component in circular bioplastic systems.

Balancing feedstock state and scalability in PHA production

Organic waste streams occur in different physical forms, and their state strongly influences the choice of suitable processing and valorisation pathways. Liquid wastes are generally well-suited for fermentation-based processes, including the production of biopolymers. In contrast, solid wastes are commonly applied in anaerobic systems for biogas generation and can also undergo physical or enzymatic pretreatments to release valuable macro- and micronutrients for subsequent reuse in other bioprocesses[43]. The choice of waste feedstock state has profound effects on PHA processing. Liquid wastes (e.g., waste oils, glycerol-rich residues, wastewater sludge) can generally be fed directly into fermentation, making handling and mixing straightforward[44]. One study showed that fed-batch feeding with thermally liquefied pork fat produced more than 45 g/L PHA (about 70% polymer content), but this was only achieved after optimizing mixing and using an emulsifier-free feeding approach[45]. Similarly, waste cooking oil generally mixes easily in aerobic reactors and can support high biopolymer accumulation. However, liquid wastes can be highly variable. Waste cooking oil from heterogeneous sources often needs enzymatic hydrolysis and emulsification[44]. Recycling protein-rich liquid streams demonstrates a circular economic approach in PHA production. The liquid stream generated during PHA production, containing microbial proteins, can be reused as a nutrient feedstock for subsequent production cycles. This minimizes the need for fresh nutrients, reduces waste, and supports a closed-loop, sustainable process[46].

Despite its advantages, liquid waste also presents challenges. Variability and impurities often require pretreatment, and inconsistent composition can lead to unstable yields. Solid waste streams such as lignocellulosic residues, food waste, and animal-derived fats require additional pretreatment before they can be used. These materials must be broken down or converted into a liquid form through steps such as mechanical size reduction, chemical or enzymatic hydrolysis, and detoxification to release fermentable sugars or fatty acids. For instance, solid animal fats need emulsification or heat-based liquefaction before feeding, and remaining solid particles must be removed to prevent equipment fouling. These extra processing requirements increase system complexity and can hinder large-scale implementation[44]. Saad et al. noted that the presence of solids in fat-based feedstocks complicates downstream processing, thereby limiting their scale-up potential[47]. Many PHA processes use low-cost or even negative-cost substrates, such as agricultural residues or spent grains. Mixed microbial cultures can handle these variable feeds and improve sustainability, but these microbial cultures typically produce only simpler PHAs, such as PHB or PHBV copolymers[48].

In summary, scaling up PHA production from organic waste involves balancing sustainability, process stability, and economic feasibility. Although using solid and mixed waste streams improves circular economy performance and lowers raw material costs, it also creates challenges. These wastes often vary in composition, may contain contaminants, and can lead to unstable or inconsistent fermentation results[49]. In addition, Organic waste streams vary seasonally and by source. Their low sugar content and potential toxins can limit microbial growth[50]. At the laboratory scale, variations in waste composition can be managed through careful monitoring and pretreatment. However, at an industrial scale, changes in substrate quality can reduce process stability, cause production interruptions, and increase operating costs. Pretreatment steps such as hydrolysis, detoxification, emulsification, or liquefaction require additional equipment, energy, and investment. These extra inputs may reduce or even offset the environmental benefits expected from using waste as a resource[51].

Moreover, downstream processing remains a major scale-up bottleneck. Even if fermentation yields are high, other factors strongly affect overall costs. For example, one pilot-scale plant was able to recover 92% of the PHA with 90% purity. However, the researchers emphasized that to make the process truly profitable, energy consumption, solvent recycling, and wastewater treatment still need to be improved and optimized[52]. Polymer recovery efficiency, solvent use, wastewater treatment, and energy consumption all play major roles in process economics. At a large scale, engineering challenges become more serious. These include poor mixing, limited oxygen transfer in high-cell-density cultures, and fouling caused by solid waste residues. Studies report that oxygen-limited PHA cultures "inevitably" see reduced productivity and uncontrollable foaming[53–55]. Techno-economic feasibility depends not only on maximizing yield, but also on maintaining stable operation, meeting regulatory requirements for waste-derived products, and accounting for lifecycle carbon emissions. Pei et al. reported that at a 4 m^3 scale, precise control of temperature and foam was necessary to maintain the stability of the mixed microbial culture[56]. Therefore, moving from laboratory success to commercial production requires integrated techno-economic and lifecycle assessments, not just yield optimization. A truly scalable PHA production system must balance circular feedstocks, simple and robust engineering design, and long-term economic sustainability[57].

Solvents, cells, and sustainability: the new chemistry of PHA extraction

Developing sustainable biomaterials requires not only renewable and low-cost feedstocks but also environmentally friendly and cost-efficient downstream processes. Traditional PHA recovery methods typically involve solvent extraction or the removal of non-PHA biomass using chemicals, enzymes, or mechanical means[58] (Fig. 2). Table 2 illustrates the recovery rates and purity of different PHA extraction methods, highlighting each method's strengths and limitations. The standard approach (chloroform extraction followed by methanol precipitation) achieves high yield and purity but relies heavily on toxic solvents and energy-intensive recycling, reducing the overall sustainability of the process[59]. In this method, solvents dissolve PHA and generally do not chemically break polymer chains, so molecular weight is largely preserved[60]. Alternatives using non-halogenated solvents have shown promising results; however, their effectiveness depends on polymer type, solubility, intracellular PHA content, and extraction temperature, limiting their universal application. Meanwhile, biomass removal with surfactants or alkaline agents like sodium hypochlorite often degrades polymer quality by lowering molecular weight. To deal with these problems, eco-friendly solvents such as dimethyl carbonate, ethylene carbonate, and butyl acetate are becoming preferred options. These methods use halogen-free solvents to weaken the cell wall and release PHA, while alcohols and noncyclic ketones can dissolve PHA specifically without affecting the rest of the cell components[49]. Using alkali solutions is also considered a highly cost-efficient method for PHA recovery[61]. Alkali-based PHA extraction involves treating the cell pellet with NaOH or KOH, followed by centrifugation to obtain PHA granules, which are then washed with water. This approach provides efficient cell lysis, easy availability of alkaline chemicals, and a good cost–benefit balance[49]. A controlled NaOH or KOH treatment usually preserves polymer weight, because it mainly hydrolyzes cell components, not PHA. However, if the alkali is too concentrated, hot, or applied too long, ester bonds in PHA can hydrolyze, lowering molecular weight[62]. Researchers note that alkaline digestion provides a "green extraction route" with minimal polymer damage because, unlike chlorinated solvents or oxidants, NaOH is a non-halogenated reagent and is not volatile. It poses fewer environmental and health risks during use. Waste streams from NaOH extraction consist mainly of salt water and biomass residues, which are easier to handle or treat compared to organic solvent wastes[3]. In addition, alkaline treatment is very effective at breaking cells open and releasing PHA, often resulting in high recovery percentages of the polymer. Studies on both pure cultures and mixed microbial cultures show NaOH can recover the majority of PHA present. For example, one comparative study found NaOH digestion achieved up to 94.7% PHA recovery efficiency from the biomass[60]. NaOH is cheap; the overall downstream cost per kilogram of PHA is reduced relative to solvent extraction. Indeed, economic analyses have shown that cell-lysis methods with alkali or

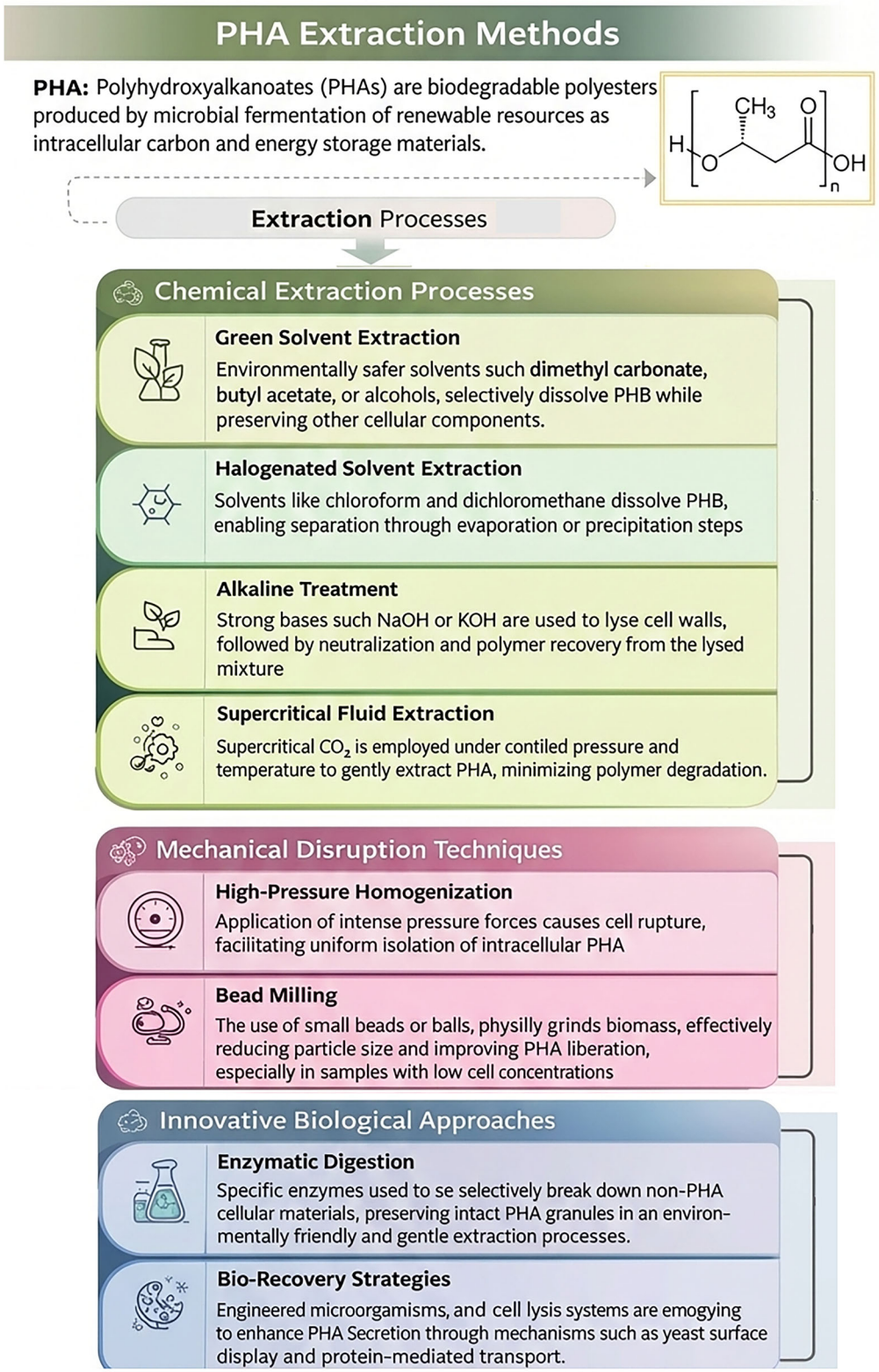

Fig. 2 | Sustainable strategies for PHA recovery and purification. A comparative overview of emerging extraction and recovery routes for polyhydroxyalkanoates (PHAs), spanning *chemical, mechanical, and biological* domains. Chemical extraction processes, including green solvent extraction, halogenated solvents, alkaline treatment, and supercritical fluid extraction, offer varying balances of yield, polymer integrity, and environmental impact. Mechanical disruption techniques like bead milling, high-pressure ultrasonication, and homogenization provide solvent-free alternatives suited to scalable, continuous operations. Innovative biological approaches, including enzymatic digestion, bio-recovery using microbial enzymes, and mealworm-assisted biodegradation, represent the next generation of low-impact, circular extraction strategies. The gradient illustrates the transition from traditional, solvent-intensive methods toward integrated, bioinspired recovery systems aligned with circular bioeconomy principles.

Table 2 | Comparison of PHA extraction methods in terms of recovery, purity, advantages, and limitations

Method	Recovery Rate (%)	Purity (%)	Energy Use	Advantages	Limitations	Decision Guidance	Ref.
Halogenated Solvents	99	95	Moderate-High	Highest recovery and purity; highly effective PHA solubilization	Uses toxic chlorinated solvents; serious environmental and health hazards	Use only when maximum purity and recovery are critical and environmental impact is not a priority	61
Green Solvents	90	92	Moderate	Good recovery/purity; more eco-friendly than halogenated solvents	Require large solvent volumes and high cost; scale-up challenges	Use when high purity is required with reduced toxicity and moderate scale is acceptable	77
Alkali (NaOH/KOH)	96.8	88.6	Low-Moderate	Very high recovery; inexpensive reagents; no organic solvents	Lower purity due to residual cell contaminants	Choose for large-scale, low-cost, solvent-free recovery when moderate purity is acceptable	78
Bead Mill	85	≈85	Low-Moderate	Low energy consumption; simple mechanical process	Requires multiple grinding cycles; may not fully lyse cells	Use for solvent-free recovery when energy use must be minimized and moderate purity is sufficient	72
Ultrasonication	88	≈85	High	Efficient solvent-free disruption; improved cell breakage	Risk of PHA chain degradation; requires optimization (multiple pulses)	Use when chemical-free recovery is needed and polymer degradation can be controlled	61
Supercritical fluid extraction (CO_2)	63	98	Very High	Extremely high purity; solvent-free extraction	Low recovery; very energy-intensive and costly equipment	Use when very high purity is needed, and cost or energy use is less important	79

surfactants have significantly lower costs compared to solvent-based recovery[58]. This favorable cost-benefit ratio of alkali extraction is a major reason it's attractive for large-scale use[49]. Although solvent extraction is effective, it requires large amounts of chemicals, which increases costs and poses environmental risks. Building on this, mechanical cell disruption methods, as a polymer-independent approach for PHA recovery that avoids polymer damage and uses no solvents, have been proposed[63]. A range of mechanical approaches can be used to rupture microbial cells, including bead milling, ultrasonication, and high-pressure homogenization (HPH). Among these, HPH has gained considerable attention because the intense shear and cavitation generated during the process effectively break open cells and free the accumulated PHA. This technique is highly adaptable and can be scaled for continuous, large-volume processing across different microbial systems[63,64]. Previous research indicates that HPH can significantly increase the yield of extracted PHA while also improving key characteristics such as purity, clarity, thermal stability, and mechanical strength. Typically, HPH is used in conjunction with chemical or enzymatic methods to maximize cell lysis and streamline the overall PHA recovery process[65]. On the other hand, HPH is considered a potentially cost-competitive and practical way to recover PHA, especially for large-scale and environmentally friendly production. It reduces costs by avoiding the use of expensive solvents and enzymes, allows high PHA recovery with little damage to the polymer, and uses common industrial equipment that can run continuously[66,67]. The main operating cost for HPH is energy. However, its cost-effectiveness depends strongly on operating conditions, since energy demand can increase substantially with higher pressures and multiple passes[68]. Despite this, the overall cost can remain balanced by the high recovery yield and the lack of solvent recovery steps. A bead mill is a straightforward and widely used technique that uses a chamber filled with small beads and rotating parts to break the cells[69]. The main drawbacks of this method are the long processing time and the large number of factors to be optimized[67]. Ultrasound treatment has also been shown to be an effective method for disrupting cells and releasing PHA[70], but it has high energy intensity per volume. Ultrasonication has been described as a cost-intensive method that is less explored for large-scale PHA extraction[71].

Biological methods for PHA extraction rely on viruses or other living agents to break open cells and release the polymer. Biological routes fully preserve polymer molecular weight[72]. Early research found that adding lytic bacteriophages to PHA-producing bacteria can make the cells burst and release PHA. The phages multiply inside the bacteria and, at the end of their life cycle, break open the cell wall. This releases the PHA particles so they can be collected. This approach was one of the earliest biological methods used to recover PHA[73]. Instead of using whole viruses, researchers have used lysis genes taken from bacteriophages and inserted them into PHA-producing bacteria to make the cells break. For example, the φX174 bacteriophage gene E was added to *Escherichia coli* engineered to generate PHA. Once the cells had accumulated enough PHA, this gene triggered self-lysis, releasing the polymer[74]. These virus-based strategies preserved PHA molecular weight (no severe polymer degradation) and offered a controllable release mechanism, although efficiency can vary[74]. More recent strategies have involved predatory bacteria, rats, and mealworms for cell disruption[73,75]. The predatory bacterium *Bdellovibrio bacteriovorus* initially yielded 60% PHA recovery, which increased to 80% in *Pseudomonas putida* when mutant strains lacking PHA depolymerase activity were used[73]. To improve yields, researchers created mutant *B. bacteriovorus* strains lacking PHA-degrading enzymes. Using a mutant predator unable to digest medium-chain-length PHA, the PHA recovery from a *Pseudomonas putida* host increased from ~60% to about 80%[72]. Enzymatic and biological methods preserve polymer molecular weight and achieve good recovery yields, but they are complex, requiring multiple sequential steps that lengthen the extraction process. Additionally, the need for pure or enzyme cocktails increases the overall cost of extraction[70].

In summary, several methods exist for PHA extraction, each with distinct advantages and limitations. Traditional solvent-based approaches achieve high yield and purity but involve toxic solvents and energy-intensive

processes. Green solvents offer more environmentally friendly alternatives, though their efficiency can depend on polymer type and process conditions. Mechanical methods allow polymer-independent extraction but may require additional steps to improve purity. Biological methods are sustainable and innovative but remain difficult to scale industrially. Alkali-based extraction stands out as a highly appropriate and sustainable method for PHA recovery. It achieves a high yield of polymer with high purity[60], avoids the major drawbacks of halogenated solvents[3], and is cost-effective and scalable for industry[49]. From regulatory and industry viewpoints, alkali extraction is generally more acceptable than solvent-based methods. Sodium hydroxide is a common industrial chemical with well-known safety protocols; its wastes are easier to treat than organic solvent waste[60]. As long as conditions are controlled to prevent polymer hydrolysis and any residual impurities are addressed with simple post-treatments, alkali extraction provides an excellent compromise among the various methods.

From data to biopolymer: artificial intelligence in the optimization of PHA production

Given the complex, data-rich nature of biorefineries and their need for sustainability and economic efficiency, optimizing every stage of their processes is very important. Traditional methods often cannot handle the complicated interactions and large data sets. New data-driven tools, along with Industry 4.0 technologies like automation, digitalization, Big Data, and Artificial Intelligence, can help improve efficiency and meet sustainability goals.

AI approaches in PHA production can be categorized based on their targets. Some models focus on bioprocess optimization, using data-driven or hybrid models to monitor fermentation parameters and maximize PHA yield and productivity. Other applications address polymer property prediction and design, using molecular descriptors and ML to forecast PHA material properties such as melting temperature or mechanical strength, and develop new biopolymers. A third category is plant-level techno-economic optimization, where process models integrate reaction yields, extraction methods, energy use, and cost factors across the whole production facility. Together, these domains illustrate how AI can operate at multiple scales, each requiring different data and modelling approaches[76,77]. Figure 3 shows how Industry 5.0 tools, such as digital technologies and machine learning (ML), can be combined to design improved PHA bioplastics. It outlines how data-driven modelling, polymer screening, and experimental updates work together to make PHA development more efficient.

Developing an effective feeding strategy for PHA production often relies on mathematical models that describe process behaviour, but creating these models can be difficult when the system is complex or not fully characterized. Simpler statistical methods, such as response surface methodology (RSM), can be applied but may not effectively capture the intricate relationships between multiple process variables[78]. Artificial intelligence approaches, particularly artificial neural networks (ANNs), provide a more powerful alternative by learning nonlinear patterns directly from data without requiring detailed process knowledge[79]. Research has shown that ANN models achieve higher prediction accuracy than conventional statistical techniques, though proper tuning and validation are essential to maintain model reliability[80]. For instance, Laurence et al.[81] successfully demonstrated that supplementing sucrose with sunflower oil and applying a drain-and-fill feeding strategy significantly enhanced PHA production by *C. necator*. A hyperparameter-optimized ANN model accurately predicted PHA yields based on process variables, enabling data-driven optimization of feeding strategies. Overall, the integration of experimental and AI-based approaches marks a key step toward smarter and more efficient bioplastic production. The major achievement of the study of Lhamo et al. is the successful implementation of an Artificial Neural Network (ANN) optimized with a Genetic Algorithm (GA) to model and optimize PHA production by *Cupriavidus necator* using acetic acid and sucrose as mixed carbon sources. The GA-ANN model demonstrated a strong predictive performance (R^2 = 0.935), significantly outperforming the traditional polynomial model (R^2 = 0.301), and effectively captured the nonlinear interactions between substrate concentration and timing of addition. Through this approach, the study accurately identified optimal conditions for maximizing PHA yield, offering a data-driven strategy for process improvement[82]. In another study, RSM combined with a genetic algorithm (GA) was successfully employed to optimize the production of PHAs using low-cost kitchen and agricultural wastes as carbon and nitrogen sources. By systematically analysing the effects and interactions of key factors, the RSM–GA approach identified the optimal concentrations of watermelon rind and pulse peel, leading to a significant increase in PHA yield (78.6%). This demonstrates that RSM–GA is an effective and predictive tool for enhancing microbial PHA production, minimizing trial-and-error experimentation, and reducing production costs while promoting sustainable waste utilization[78]. Luna et al.[83] developed a hybrid model combining first-principles and ML to optimize continuous PHA production by *Pseudomonas putida* GPo1. This model accurately predicted process behaviour under different nutrient limitations and operating conditions, demonstrating its potential as a reliable tool for improving PHA yield and process efficiency. In addition, the power of ML in predicting and optimizing the thermal properties of PHAs, specifically their melting temperature, as illustrated by Bejagam et al.[84], using molecular descriptors and experimental data, the models accurately forecasted PHA behaviour and enabled data-driven design of new biopolymers. This approach increases PHA development with tailored properties for sustainable applications. Ramos et al.[85] developed a Mixed Integer Nonlinear Programming (MINLP) model to optimize the design of a PHA production plant, integrating multiple carbon sources such as glycerol, starches, sucrose, and molasses. By evaluating four extraction methods and incorporating capital, mass, and energy balance constraints, the model identified the sugarcane-enzyme process as the most efficient configuration, achieving the highest net present value with low energy consumption.

However, these approaches have limitations before AI-driven PHA optimization can be considered industrially transferable. Bioprocess and materials datasets are often expensive to collect, so models may be trained on limited, context-specific data[86]. Complex models like ANNs can overfit when data are limited[87], as a result, they may fail to generalize when applied to different strains, substrates, reactor designs, or larger scales[88]. Another major limitation is the lack of sufficient and consistent data. Bioprocess datasets are usually small, specific to certain microbial strains, and collected under controlled laboratory conditions. Because of this, machine learning models may fit too closely to the limited data (overfitting) and may not perform well when applied to different strains, feedstocks, reactor types, or larger production scales. As a result, these models are often difficult to transfer from one production system to another[89].

Scalability and regulatory challenges also make it difficult to transfer AI models from the lab to industry. When a bioprocess is scaled up, new factors appear such as temperature and oxygen gradients, different reactor designs, and more complex microbial interactions that were not present at laboratory scale. Because of this, AI models often need to be retrained or revalidated at each new scale[90]. In practice, automating a full biomanufacturing process usually requires multiple specialized AI models, often one for each critical process variable, rather than a single universal model. Managing, updating, and validating many interconnected models each designed for a specific product and equipment setup creates a significant operational challenge. In addition, strict biomanufacturing regulations increase the complexity. Regulatory authorities such as the U.S. Food and Drug Administration and the European Medicines Agency have introduced guidance to support the use of AI within Good Manufacturing Practice (GMP) frameworks. However, companies must still provide clear evidence of traceability, reproducibility, and safety for every AI-driven decision, which adds substantial validation requirements[91,92].

PHAs have flexible properties that make them useful in many fields, but more research is still needed to improve extraction processes and achieve higher yield and purity. For instance, conventional solvent-based extraction yields high-purity polymer but demands large volumes of toxic

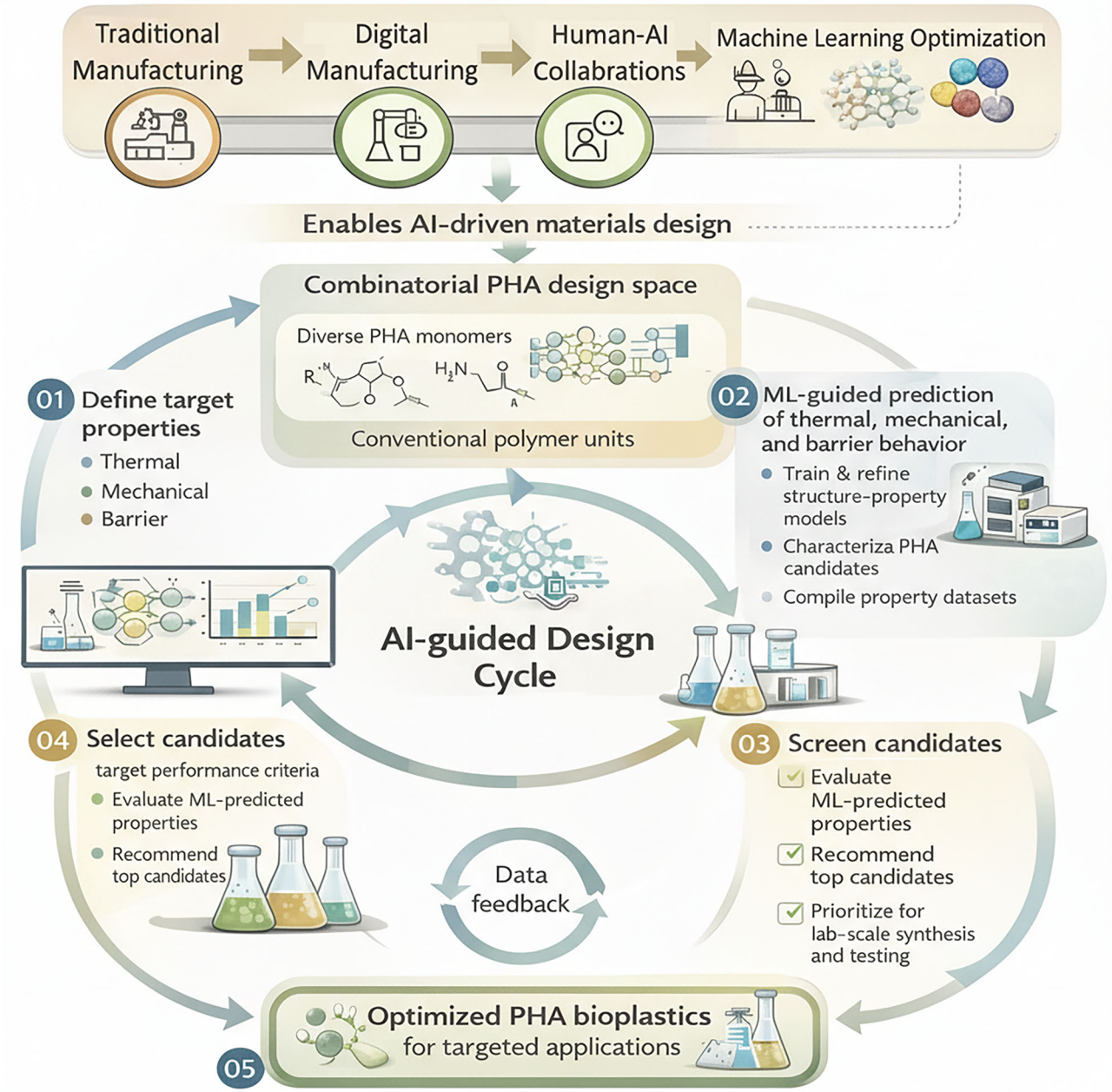

Fig. 3 | Integration of industrial evolution with an AI-enabled workflow for engineering next-generation PHA bioplastics. The top panel illustrates the technological progression from Industry 1.0 to Industry 5.0, culminating in human–machine collaboration and intelligent manufacturing. This framework underpins the lower pipeline, where diverse PHA monomers and conventional polymer units are combinatorially paired and evaluated through predictive machine-learning (ML) models. Iterative data refinement, structure–property prediction, and performance-based screening enable the identification of high-performance PHA formulations and the selection of candidates for synthesis and experimental validation, ultimately guiding optimized biopolymer design.

solvents and energy-intensive solvent recovery steps, which drives up production costs[3,58,93,94]. In contrast, enzymatic and other "green" extraction methods avoid hazardous chemicals yet often suffer from lower PHA recovery or high operational costs, underscoring the need for further innovation to improve extraction efficiency and polymer purity[63,95]. Approaches such as genetic modification, better control of growth conditions, and the use of modern tools, including artificial intelligence, ML, MINLP, ANNs, and RSM, can greatly boost PHA production. New technologies must be carefully tested and compared through proper validation, life-cycle assessment, and testing at different scales. This ensures that innovations deliver real industrial and environmental benefits. If techno-economic analysis, digital systems, and regulatory requirements are not properly integrated, AI-based optimization may stay limited to laboratory research instead of leading to real transformation in large-scale bioplastic production.

Signal to degradation: intelligent end-of-life design and lifecycle feedback for PHA systems

Plastic pollution keeps increasing because people often ignore how resistant plastics are to degradation and the lack of proper end-of-life options. Using biodegradable plastics and disposing of them with organic waste can help reduce the amount of waste and support environmental sustainability. However, to understand their true impact, it's important to look at their full life cycle. In some cases, petroleum-based plastics with efficient recycling systems can be more sustainable than certain bioplastics when their entire life cycle is considered[96]. PHA's versatility makes it an important material for

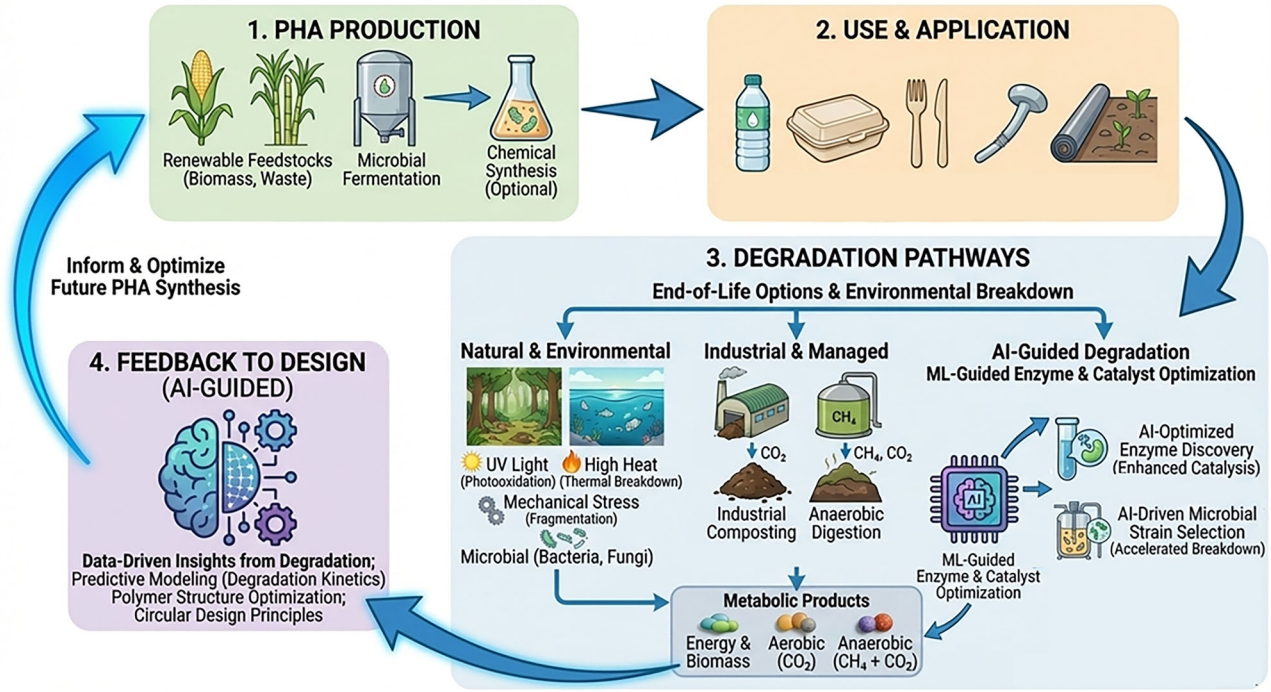

Fig. 4 | Overview of polyhydroxyalkanoate (PHA) degradation pathways. PHAs are broken down by environmental and microbial processes into smaller molecules, which are further metabolised by microorganisms to produce energy and end products such as CO_2 (aerobic) or CH_4 and CO_2 (anaerobic).

advancing a circular economy. It can be produced from renewable or waste-based resources and used in many different applications. Since it is also biodegradable at the end of its life, PHA offers a more sustainable alternative to conventional plastics[97]. The end-of-life pathway of PHAs critically affects their carbon footprint. Composting and landfilling of PHA leads to the release of the polymer's carbon as CO_2 (and CH_4 under anaerobic conditions). For example, a simplified global scenario estimates that composting all plastic packaging as PHA (≈ 140 Mt/yr) would emit on the order of 230 million metric tons CO_2 per year[98]. This CO_2 mainly comes from plants or organic waste that absorbed carbon from the air during PHA production. In contrast, conventional plastics release carbon from fossil fuels. In other words, producing PHA displaces fossil-based plastics and their CO_2 emissions, but releasing the carbon again through composting can reduce this benefit. To achieve better carbon savings, PHAs should not rely only on composting. Recycling, reuse in closed systems, or low-energy breakdown methods can help keep the carbon in use for longer[49]. PHA can break down through different pathways, such as exposure to light and oxygen, microbial activity, catalytic reactions, heat, or mechanical stress[99]. Figure 4 illustrates different PHA degradation pathways.

Microbial degradation is one of the primary pathways through which PHAs are broken down in natural environments. In this process, different bacteria and fungi release enzymes that break PHA polymers down into smaller molecules such as monomers and oligomers. These degradation products are subsequently taken up and metabolized by the microorganisms as carbon and energy sources. Many types of microbes capable of breaking down PHA have been found in diverse environments, including soil, freshwater, marine systems, and even extreme places like hot springs and polar regions. This shows how adaptable these organisms are and highlights the natural ability of microbial cultures to control PHA degradation in the environment[100]. Mechanical degradation happens when physical actions such as rubbing, cutting, or grinding break the polymer into smaller pieces without changing its chemical structure. These smaller fragments are then easier for other degradation processes to act on.

Thermal degradation occurs when the polymer is exposed to high heat, causing the chains to break randomly and form smaller molecules like oligomers and monomers. While this method works, it requires a lot of energy and can produce unwanted by-products[100]. Photooxidative degradation happens when the material is exposed to light, especially ultraviolet (UV) radiation. The UV light creates free radicals that break the polymer chains. This process is generally slow and strongly influenced by how much UV light is present and how long the exposure lasts[99]. Finally, Catalytic degradation accelerates PHA breakdown through the action of enzymes, transition metal ions (e.g., in Fenton reactions), or nanozymes that specifically target ester bonds in the polymer chain. While this approach enhances degradation efficiency, it often requires costly and specific catalysts[101]. To overcome these limitations, recent research has turned to ML to accelerate enzyme discovery and improve catalytic performance. By integrating computational modelling with targeted experimental testing, ML-enabled workflows can screen thousands of enzyme variants, making data-driven design the new standard in enzyme engineering[102]. Although ML is only beginning to be applied to PHA biodegradation, emerging studies demonstrate its potential. For example, one study used ML models to predict thermal properties of diverse PHA homo- and copolymers based on molecular descriptors, enabling rapid screening of multicomponent structures and identification of optimal compositions. While focused on structure–property relationships rather than degradation kinetics, this work illustrates how ML can efficiently navigate complex PHA chemical spaces and guide experimental efforts. Such approaches are now being extended toward predicting enzyme–polymer interactions and degradation behaviour, signalling a growing role for ML in designing more degradable PHA systems[84]. In addition, broader research has shown that AI can successfully optimize microbial and enzymatic degradation pathways across various plastics. For instance, recent work demonstrated that AI tools can identify high-performance microbial strains and enhance enzyme activity for plastic breakdown, highlighting the wider applicability of AI-driven biodegradation strategies. These insights further reinforce the potential of integrating ML with microbial pathways to accelerate the development of more efficient PHA degradation systems[103]. Predictive machine learning models are an emerging research area that can estimate polymer degradation based on molecular structure. These models can support polymer design and lifecycle optimization by helping ensure that new materials achieve both functional performance and controlled end-of-life behaviour. For example, ML-based

screening of polymer compositions or enzyme–polymer interactions can help identify formulations that degrade efficiently under specific conditions while still maintaining the required material properties[104,105]. This data-driven design approach effectively closes the loop between polymer synthesis and end-of-life, aligning material development with circular economy objectives and fulfilling the intelligent biomanufacturing vision.

In summary, PHAs offer strong potential as sustainable materials, but their ultimate environmental benefit depends on intelligent end-of-life design and a clear understanding of their degradation pathways. Emerging ML tools are beginning to accelerate catalyst discovery and polymer optimization, pointing toward a future where PHA systems can be engineered for more predictable, efficient, and circular degradation behaviour.

Conclusion and future perspective

Polyhydroxyalkanoates (PHAs) have emerged as promising bio-based alternatives to conventional plastics, offering a unique combination of biodegradability, biocompatibility, and functional versatility. Recent years have seen significant advancements in microbial engineering, the development of green extraction and processing technologies, and the valorization of waste-derived feedstocks. Meanwhile, PHA-based materials' mechanical, thermal, and barrier qualities have been enhanced by the addition of renewable fillers like cellulose, biochar, and microalgae-derived components, increasing their use in food packaging, agriculture, biomedical devices, and emerging manufacturing technologies. By enabling data-driven process design, predictive modelling, and enhanced resource efficiency, the integration of artificial intelligence (AI), machine learning, and hybrid optimization techniques has further strengthened PHA biomanufacturing. Despite these developments, several significant obstacles still stand in the way of PHAs' widespread use and commercialization. High production costs, which are mostly caused by feedstock costs, inefficient processes, and energy-consuming downstream recovery, continue to be an important limitation. The presence of additives, processing conditions, and monomer composition can all have considerable effects on material performance, which commonly result in brittleness, limited flexibility, or inconsistent properties across applications. Furthermore, current extraction methods still have to make trade-offs between polymer purity, molecular weight preservation, cost, and environmental impact, and the use of complex or waste-derived materials introduces variability in fermentation performance. Most importantly, there is still uncertainty about what happens to PHAs at the end of their life, how quickly they break down in different environments, and how additives (like fillers or compatibilizers) affect their degradation. This makes it difficult to fully trust the circular, eco-friendly promise of PHA systems. Therefore, with the help of developments in synthetic biology, metabolic engineering, and green chemistry, future research should concentrate on the logical design of PHAs with adjustable and predictable structure-property-degradation relationships. The development of next-generation PHA blends and composites can be sped up with the help of AI-guided materials informatics and process optimization, which enable quick formulation screening, better process control, and less reliance on trial-and-error experimentation. In addition, the development of AI-enabled circular materials ecosystems is what lies ahead of PHAs alone. By integrating PHAs into these intelligent systems, waste can be decreased, resources will be conserved, policy decisions will be guided, and ultimately, a more efficient and sustainable global materials economy may be achieved.

Data availability

No datasets were generated or analysed during the current study.

Code availability

Not applicable since there is no computer programming/coding was used for this work.

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Competing interests

The authors declare no competing interests.

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