REVIEW

Poly(hydroxyalkanoates): Emerging Biopolymers in Biomedical Fields and Packaging Industries for a Circular Economy

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Abstract

Poly(hydroxyalkanoates) (PHAs) are a class of sustainable, bio-based thermoplastic polymers with attractive physiochemical properties, including non-toxicity, biocompatibility, elastomeric behavior by design, and piezoelectric characteristics. In the ongoing effort to reduce plastics waste, PHAs can play a substantial role due to their inherent biodegradability free of microplastics, customizable properties, and versatile applications. This includes their tremendous potential in a broad range of biomedical applications. Biomass-based materials have recently gained great interest in the health sector, given the vast amount of interdisciplinary research in bioengineering and medicine. Implantable biomaterials should not elicit any negative response at the implantation site, which differentiates them from general-purpose polymers. PHAs do not induce any thrombosis or antigenic response even after being in contact with blood in the human body during long-term use. The biocompatibility of PHAs is also a key factor in the rapid growth and proliferation of tissues onto and within these materials when served as tissue engineering scaffolds. By application, the biomedical field was estimated to be the second-largest market share for PHAs, in terms of volume, in 2022. While PHA-based materials bring forth a broad range of opportunities, they also present challenges that have limited their widespread use and a greater market share. A better understanding of their physiochemical properties and biodegradation rates, production challenges, and the need for cost-effective strategies are some of the hurdles that need to be addressed. This review paper provides an overview of the commonly used PHA homopolymers and copolymers in biomedical fields and packaging industries. The introduction of the manuscript presents the concept of bioplastics and their environmental significance, highlighting the urgent need for alternatives to conventional fossil-based plastics. The next sections briefly cover the synthesis, properties, as well as homopolymer and copolymer formulations, followed by the application of PHA-based materials in the biomedical field. Current opportunities and challenges, together with some insight into the future gathered from the published studies, have been brought in the concluding section of this paper.

Keywords Implantable biomaterials · PHA homopolymer · PHA copolymer · Sustainable bioplastics · Microplastics

Introduction

Synthetic polymers have generated a substantial amount of waste on the globe. Their main disadvantage is that most of these materials are non-biodegradable and can accumulate in the environment**.** Globally, the annual production of plastics has reached 311 million tons, and it is estimated that the production level might reach 500 million tons by 2050 [1]. If the current production and waste management systems continue unaltered, the plastics accumulated in the environment will reach 12 billion metric tons by 2050 [2]. At present, the production of fossil-based materials, particularly the single-use plastics, is causing the depletion of limited natural resources and leads to the emission of greenhouse gases, climate change, release of microplastics, and pollution of terrestrial and aquatic environments. Therefore, it is evident that there is an urgent need for sustainable alternatives to substitute for the current nonrenewable resources [3].

A class of widely studied alternative is bioplastics. The prefix 'bio' in bioplastics has been interpreted in different ways (or a combination thereof): (1) the monomers were initially derived from renewable resources (biomass) and subsequently polymerized through chemical mechanisms; (2)

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the polymer itself was extracted from biomass; (3) the polymer or the plastic is biodegradable, although the processing of a polymer to turn it into a plastic product might affect the original biodegradability; (4) the material was produced through biological processes [4, 5] (Fig. 1). In general, it is discouraged to use 'bioplastics' for fossil-derived degradable plastics [5]. Thus, bioplastics are considered to be those polymers produced from plants, or the biological materials that are generally synthesized by microorganisms [6].

Replacing synthetic polymers with green, biodegradable bioplastics could be a sustainable approach to tackling current plastics pollution [1]. This transition can lead to a circular economy by offering environmentally sustainable alternatives to fossil-based plastics [7]. Considering the overall plastics production worldwide, the global market share of bioplastics is currently between 1 and 2%. Nevertheless, a promising steady growth of the global production capacities for bioplastics has been reported, from 1.9 million tons in 2019 to 2.4 million tons in 2021. It is forecasted that the global production of bioplastics may even triple by 2026 and eventually exceed a market share of 2% of global plastics production [8].

Among the currently identified bioplastics, poly(hydroxyalkanoates) (PHAs) are a class of sustainable bio-based, biodegradable, and thermoplastic polymers. Some estimates based on a number of life cycle studies suggest that replacing 1 kg of fossil-based plastics with PHAs could salvage 2 kg of CO_2 emissions on average and would potentially save around 30 MJ of fossil resources on an energy basis [9]. PHAs have found applications in

biomedical and pharmaceutical fields [10–12], packaging (e.g., food sector) [13, 14], and agriculture, among others [7, 15]. By application, the biomedical field was estimated to be the second-largest market share for PHAs, in terms of volume, in 2022 [16]. Commercial PHAs currently produced under various trade names with potential biomedical applications include TephaFLEX™, TephaELAST™, GalaFlex™, Phasix™, BioFiber™, MonoMax™, Biopol™, Biomer™, AmBio™, and Medpha PHA™ [9, 17, 18]. Some other products intended for general/green applications include BioGreen™, Biocycle™, Nodax™ [19], AirCarbon™, YOPP/YOPP+™, PHACT™, ENMAT™, etc. [9, 20].

Under nutrient-limiting conditions, microorganisms start accumulating PHAs as carbon reservoirs [1]. Thus, PHAs are the typical intracellular reserve products generated by various Gram-negative or Gram-positive bacteria and some extremophilic Archaea [10]. PHA granules generated by these microorganisms consist of a hydrophobic water-insoluble core of coiled PHA chains and water, which acts as a plasticizer. The PHAs stored in the cell cytoplasm (light-refractive and spherical in shape) are surrounded by more hydrophilic enzymes and structural proteins that form a membrane [10]. Biomass materials, such as PHAs, are mainly composed of hydrogen, carbon, and oxygen. As a result, these materials are easily degraded by natural microorganisms into carbon dioxide, water, and other small molecules, enabling their products to reenter the natural cycle [21]. When ingested by living organisms, PHAs are readily metabolized to non-toxic compounds in the body and are

Fig. 1 A list of fossil-based (left) and bio-based (right) non-biodegradable (top) and biodegradable (bottom) polymers. Reproduced/modified from Rosenboom et al. [5] with permission
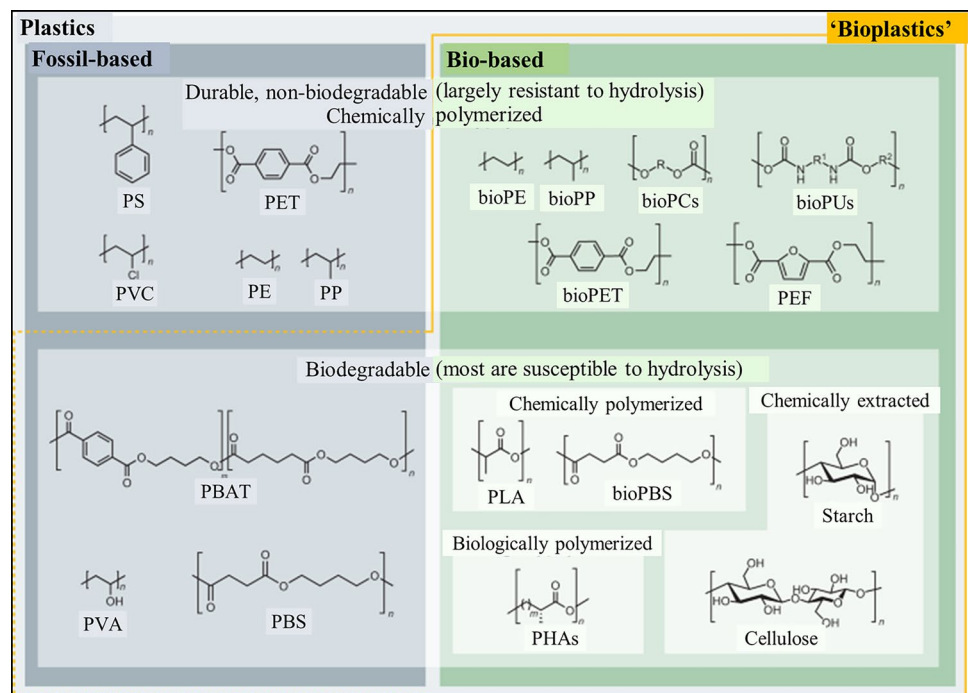
biocompatible to humans and other life forms [9, 22]. PHAs are non-toxic materials that naturally occur in human blood and tissues. New applications sought for PHAs in the medical field is due to this biocompatibility [23, 24].

PHAs have attractive physiochemical properties, including non-toxicity, biocompatibility, biodegradability, elastomeric, and piezoelectric characteristics [1]. These properties of PHAs can be tailored by altering their monomer compositions [25]. More than 160 different types of PHAs, consisting of various monomers and comonomers, have been reported [26]. Some of the most common PHAs include poly(3-hydroxybutyrate) [P(3HB)], poly(4-hydroxybutyrate) [P(4HB)], poly(3-hydroxyvalerate) [P(3HV)], copolymers of 3-hydroxybutyrate and 3-hydroxyvalerate [P(3HB-co-3HV)], and copolymers of 3-hydroxybutyrate and 3-hydroxyhexanoate [P(3HB-co-3HHx)]. Furthermore, PHAs can be blended with other polymers [27–29] or with other organic/inorganic materials to further adjust their properties [2, 29]. Extensive research has been devoted to generating knowledge on tailoring the product properties and facilitate their processing, by fine-tuning the (co)polymer composition [30] and blending with other appropriate chemical additives and polymers [9, 31].

The contribution of PHAs to the bioplastics market still represents a small percentage (i.e., 1.7% of the total amount of bioplastics produced in 2020) [16]. Despite the tremendous potential of PHAs, significant challenges to overcome still exist before PHAs find a widespread use in a variety of applications [32]. The market price of PHA bioplastics was originally 15–17 times higher than synthetic plastics. Although the efforts to reduce the production costs have been successful, the market price of PHAs is currently about three times higher compared to conventional synthetic polymers [33]. This is mainly due to the high costs of carbon source acquisition, which accounts for 30–40% of the final PHA price, despite the rapid decrease in cost in the past several years [34]. Another hurdle is the design challenges related to the identification of optimal PHA chemistries for a target application. This includes the composition and configuration of the monomers in the polymer backbone, along with the size, polarity, and type of the side chain functional groups [32]. Although PHAs cover a substantial spectrum of the properties of fossil-based plastics, these bio-based materials are not an exact match to the conventional synthetic plastics [9, 35].

Figure 2 shows a list of key historical milestones for PHAs (gray blocks), along with a few other related advancements (white blocks) that helped with the progress in research on PHAs [36]. Although the first report of a bacterial PHA inclusion dates back to as early as 1888, observed by Beijerinck [36, 37], the actual discovery of PHA is generally attributed to a research study in 1923 by Maurice Lemoigne, who reported granular inclusion bodies in *Bacillus megaterium*. These granular bodies were later extracted and identified as P(3HB) [25]. This was followed by several other studies published from 1923 until the mid-twentieth century (Fig. 2) [36]. Macrae and Wilkinson reported in 1958 that PHAs in microbial cells serve as a reserve of energy and carbon materials, which occurs only when the carbon-to-nitrogen ratio changes [38]. Beginning in 1959 marks the beginning of commercialized PHAs as environmentally friendly bioplastics, and W.R. Grace and Company was the first that attempted to produce commercial PHAs [19]. In 1982, it was reported that the properties of P(3HB) were
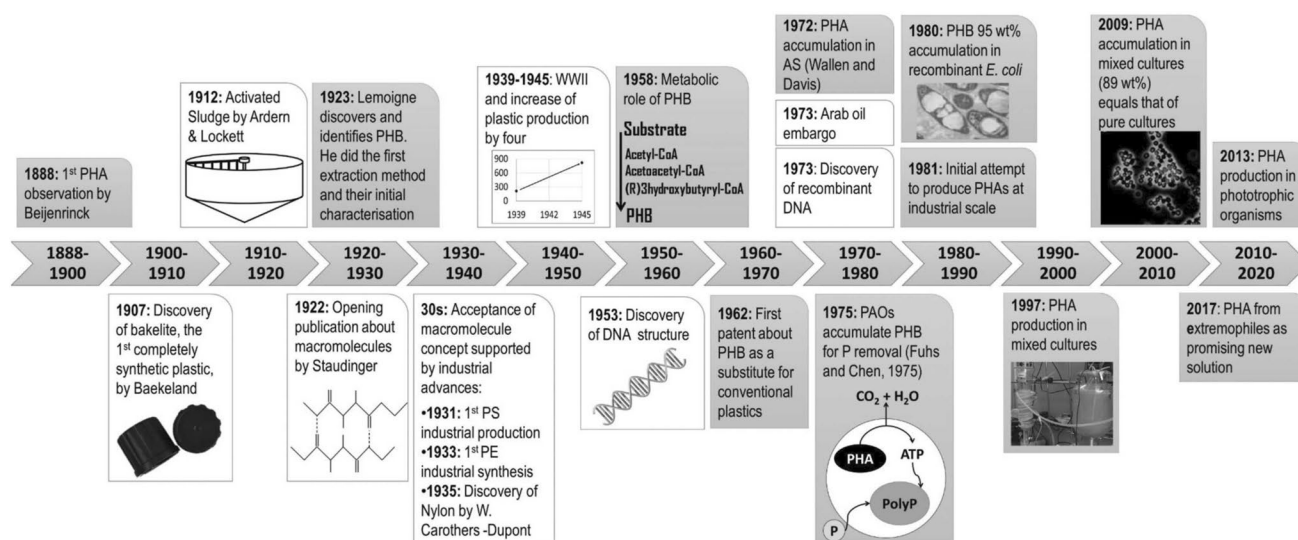

Fig. 2 Key historical milestones for PHAs (gray blocks) and other advances in related fields (white blocks) that contributed to the progress in research on PHAs. Reproduced from Palemerio-Snáchez et al. [36] under the Creative Commons Attribution license

similar to those of polypropylene [39], while another paper reported on the biodegradability and biocompatibility of P(3HB) [40]. The published research on PHAs indicates that hundreds of different types of pure culture microorganisms have been found to be the natural PHA producers, including some genetically modified strains. Some other research advancements on PHAs are also highlighted in Fig. 2 [36].

Overall, the economic feasibility and scalability of PHA production, together with the optimization of PHA chemistries to achieve optimal mechanical and thermal properties, remain some key challenges and require a paradigm shift in many areas [41]. Nevertheless, it is projected that the market share will substantially increase in the next few years [42]. According to a recent estimate, the market size of PHAs is projected to increase from 93 million (USD) in 2023 to 195 million (USD) by 2028, which represents a compound annual growth rate (CAGR) of 15.9% [16]. The foreseen growth is mainly due to the outstanding versatility of the properties offered by various members of PHA-based materials [42]. A broadly implemented production method for PHAs is the fermentation of sugar, which is sourced from agricultural materials such as sugarcane, beet, and molasses. This method is estimated to exhibit a significant compound annual growth rate (CAGR) in terms of value during the forecast period [16].

This review paper provides an overview of the commonly used PHA homopolymers and copolymers. The first sections briefly cover the history, synthesis, properties, homopolymer and copolymer formulations, followed by the application of PHA-based materials in the biomedical field. This will enable the readers to gain adequate information about the PHA-based materials before delving into their biomedical applications. More than 60 references cited were published in 2023, making this paper an up-to-date overview of the recent advances in the field. Furthermore, a summary Table at the end of this paper lists the outlines of some recently published review papers related to the applications of PHAs in biomedical fields. Current opportunities and challenges, together with some insight into the future, gathered from the published studies, have been brought in the concluding section of this paper.

Chemical Structure of PHAs

Tailoring the physicochemical and mechanical properties of PHAs can be primarily achieved by altering the monomer composition of the polymer [43]. The number of carbon atoms in 3-hydroxyalkanoate (3HA) repeat units is used to classify PHAs [25]. Those with 3–5 carbon atoms are known as short-chain length PHA (scl-PHA) [6, 26], which include 3-hydroxybutyrate (3HB) and 3-hydroxyvalerate (3HV) as shown in Fig. 3 [26]. In contrast, the number of carbon atoms in a medium-chain length PHA (mcl-PHA) ranges between 6 and 14 [6, 25]. This class of PHA repeat units includes 3-hydroxyhexanoate (3HHx), 3-hydroxyoctanoate (3HO), 3-hydroxydecanoate (3HD), and 3-hydroxydodecanoate (3-HDD), among others [25, 26, 44]. Long-chain length PHAs (lcl-PHAs) are less common and have not been extensively studied [19]. PHAs offer an enormous design space, allowing to synthesize a wide range of chemical structures with versatile material properties. This can be achieved by manipulating the diversity of side chains in the comonomers, their arrangement and sequence, as well as by varying the molecular weight of PHAs [45].

Fig. 3 Chemical structures of PHAs showing short-chain length (scl) and some of medium-chain length (mcl) repeat units. Reproduced from Taguchi and Matsumoto [26] with permission
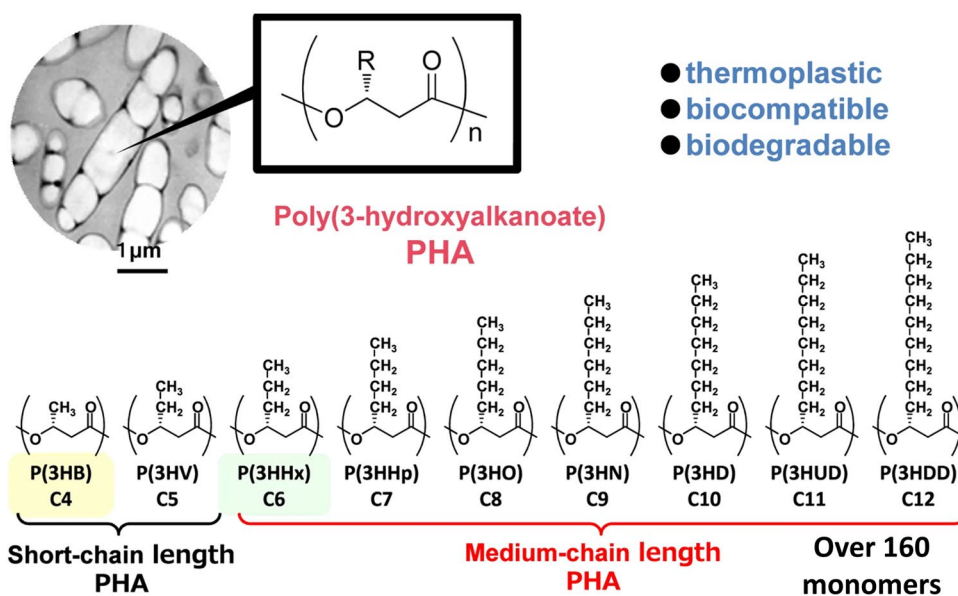
Production of PHAs

Similar to biofuels, bioplastics can be produced from a variety of feedstocks, which can be categorized into four main generations as shown in Fig. 4a [46]. The list includes edible biomass (first generation), non-edible biomass (second generation), algal biomass (third generation), and electrical-driven sources (fourth generation). This review briefly covers the first two generations (Fig. 4a). Although the first-generation feedstocks are more abundant than second-generation sources, the latter does not compete with the food industry and should ideally be the preferred option [46]. The use of waste feedstock has the dual benefit of tackling waste disposal in the environment while generating a cost-effective and sustainable process for PHA production [47].

In recent years, numerous studies have looked into the conversion of industrial by-products and waste sources into PHAs [46]. These sources include spent coffee ground oil [48], waste frying oil [49], and waste animal fat streams [46], among others. A circular bioeconomy is the ultimate goal in our societies; hence, the conversion of wastes to PHAs can greatly contribute to this goal. Nevertheless, choosing the second-generation feedstock option to reduce the cost of PHA production could adversely affect the productivity and product quality, caused by fluctuating waste feedstocks and their compositions [46, 47]. This might be due to the presence of impurities in the feedstock. Numerous studies have suggested that the waste feedstocks generated from different industries, featuring different chemical compositions, could result in varying PHA production and cell biomass [47].

Low-cost renewable carbon sources such as energy crops or waste streams, when combined with optimized fermentation strategies, can provide high-yield PHA production processes [25]. Food waste as a substrate, for partial or full substitution of glucose and other nutrients, can substantially reduce the cost of PHA production and improve their market competitiveness, compared to fossil-based plastics, and eventually lead to a circular economy [50]. Figure 4b shows the lifecycle of circular PHA production [25]. PHA-based polymers are used to manufacture consumer plastics, which will eventually biodegrade after their disposal. The cycle begins again when the biodegradation products of PHA are recovered in waste streams from composting facilities [25].

A subgroup of the second-generation feedstocks includes C1 compounds such as methane (CH_4) or synthetic gases (syngas) derived from organic waste [46]. For C1 compounds, PHA synthesis has been reported from carbon dioxide (CO_2), methanol, methane, and formate [1, 51]. Syngas is mainly composed of CO, CO_2 and H_2, and is an organic

Fig. 4 **a** Classification and examples of feedstock generations used for biotechnological processes. Reproduced from Gutschmann et al. [46]; **b** The lifecycle of sustainable PHA production. Reproduced from Bedade et al. [25] under the Creative Commons Attribution license
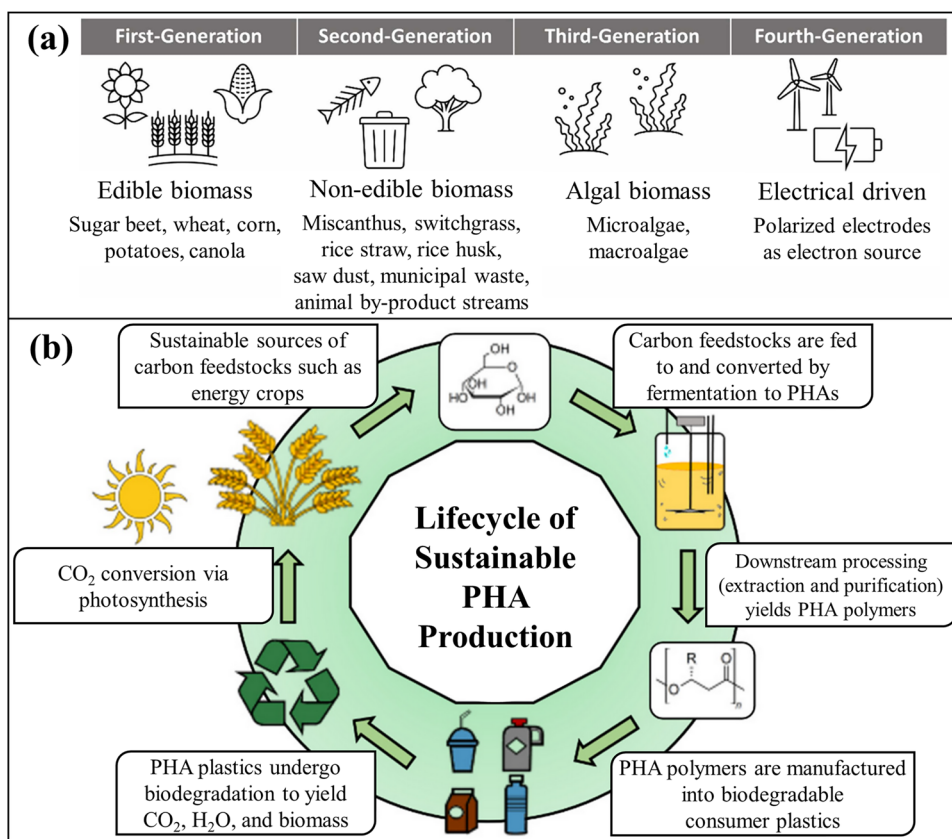
industrial waste product from petroleum refineries and other industries such as steel mills [46]. A substrate gas mixture composed of CO_2, O_2, and H_2 has been used in a recent study to produce PHAs [52]. Furthermore, a commercialized P(3HB) product (AirCarbon™) is manufactured using air and CO_2 from greenhouse gas as feedstock, currently marketed by Newlight Technologies LLC [9]. Thus, biotechnology is holding promise for transforming CO_2 emissions into biopolymers and other valuable commodity materials [26].

Wastewater as feedstock [36] and wastewater-cultivated microbes have also been used for producing biopolymers such as P(3HB), also making it a sustainable approach to wastewater treatment. These efforts include the use of mixed microbial cultures (MMC) [10, 53], which reduces the operational costs while having the potential of adapting the production to a wide range of waste substrates that could be integrated in current wastewater treatment plants [54]. The produced bioplastics in these technologies cannot be used for biomedical applications, which require stringent sterile environment during production [55]. These PHA products could still be used for industrial applications and help to address the pollution caused by single-use plastics.

Some factors that affect the production of PHAs include carbon-to-nitrogen (C/N) ratio, mode of fermentation, and fermenter operating parameters [56]. Agitation is another key factor in PHA production, since low agitation rates can lead to cell aggregation. Similarly, higher-than-optimal agitation rates may cause reduced biomass and PHA content [51]. Figure 5a shows some biological, technological, and economical challenges in PHA production [47]. Suitable pretreatment of waste feedstock, nutrients supplementation, optimization of the operating conditions, effective fermentation strategies, and employing genetic engineering tools can improve the efficiency of PHA production and make it cost-effective [47]. Figure 5b shows typical applications of PHAs that could potentially help to reduce the use of fossil-based plastics [57]. A list of commercialized PHAs, including P(3HB), P(4HB), and their copolymers, is given in Table 1 [9, 17, 18, 58].

It should be noted that more than 300 bacterial species have been reported to produce PHAs [59]. Thus, the choice of bacterial strain becomes one of the key factors in enhancing the PHA production. Some of the most widely used microorganisms include *Ralstonia, Burkholderia, Halomonas, Alcaligenes* and *Pseudomonas* sp. This is mainly because of their ability to utilize various carbon sources and produce diverse types of PHAs [59, 60]. *Pseudomonas* species are predominantly capable of mcl-PHA biosynthesis. Some bacteria, such as *Aeromonas caviae* or *Aeromonas hydrophila*, have been reported to synthesize copolymers consisting of hybrid scl-PHA and mcl-PHA building blocks [42]. Furthermore, depending on the selected microbial production strain and the renewable raw material used in
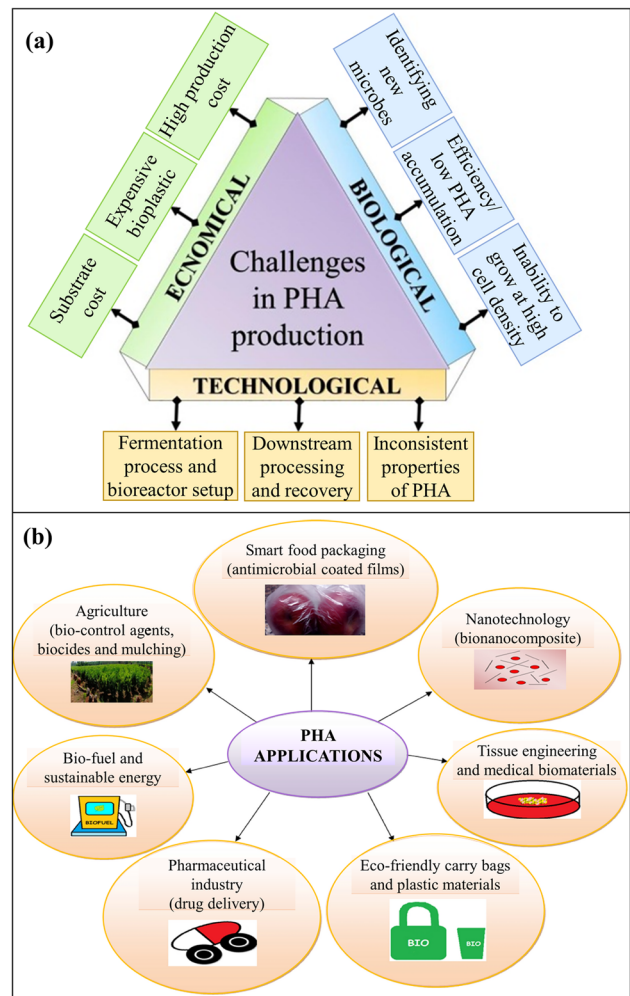

Fig. 5 **a** Some biological, technological, and economical challenges in PHA production. Reproduced from Ghanesh Saratale et al. [47] with permission; **b** Typical applications of PHAs in various fields. Reproduced from Saravanan et al. [57] with permission

the production, the properties of the produced PHAs can emulate those of both elastomers and thermoplastics [3, 31]. Investigation of different microorganisms capable of producing PHAs, and their feedstocks and fermentation processes have been the subject of extensive reviews papers [6, 50, 53, 54, 61–65] and some recent research studies [7, 66, 67].

Properties of PHA-Based Homopolymers and Copolymers

The physicochemical and thermal properties of PHAs can be altered by manipulating the type and composition of monomers in the PHA structure, repeat unit randomness, molecular weight, polydispersity, the length of carbon side chains (scl-PHA *vs.* mcl-PHA), as well as the separation between the functional group and the ester bond [62, 68, 69].

Table 1 Some commercialized PHAs, including P(3HB), P(4HB), and their copolymers. The table shows their FDA-approved applications, when applicable. Adopted/modified from Koller and Mukherjee [9], Williams et al. [17], Puppi et al. [18], and [58]

Type of PHA	Substrates (feedstocks)	Brand name	Manufacturer (city, state, country)	Remarks (e.g., FDA[†] approval)
P(3HB)	Hydrolyzed cane sugar/sucrose	BIOCYCLE™	PHB Industrial S.A. (Serrana, Brazil)	
	Sucrose	Biomer™	Biomer (Schwalbach, Germany)	
	Crude biogas (CH_4, CO_2, H_2S)	YOOP+™	Mango Materials (Redwood City, USA)	
	CH_4 and CO_2 from greenhouse gases	AirCarbon™	Newlight Technologies LLC (Huntington Beach, USA)	FDA approved for food contact
	Waste cooking oil	Hydal PHA™	Nafigate Corporation (Prague, Czech Republic)	FDA approved for food contact
P(4HB)	Not disclosed	TephaFLEX™	Tepha Medical Devices, Inc., (Lexington, USA); Becton, Dickinson and Company (BD)	FDA approved for biomedical use as implant material
	Not disclosed	GalaFLEX™	Galatea Surgical, Inc., (Lexington, MA, USA); Becton, Dickinson and Company (BD)	FDA cleared for the repair and reinforcement of soft tissue
	Not disclosed	Phasix™	Becton, Dickinson and Company (BD) (Franklin Lakes, NJ, USA)	FDA cleared for the repair and reinforcement of soft tissue
	Not disclosed	Phantom Fiber™	Wright Medical Group, Inc. (Memphis, TN, USA), Stryker Corporation	FDA cleared for use in general soft tissue approximation and/or ligation
	Not disclosed	BioFiber™	Wright Medical Group, Inc. (Memphis, TN, USA), Stryker Corporation	FDA cleared for general soft tissue approximation and/or ligation
	Not disclosed	MonoMax®	B. Braun AG (Melsungen, Germany)	FDA cleared as an absorbable suture
P(3HB-*co*-4HB)	Glucose and 1,4-butanediole (4HB precursor)	SoGreen™	Tianjin GreenBio Materials Co. Ltd. (Tianjin, PR China)	
	Sugar (sucrose or dextrose)	PHACT A1000P™	CJ Bio (CJ Biomaterials) (Seoul, Republic of Korea)	FDA approved for food contact
	Not disclosed	TephaELAST™	Tepha Medical Devices, Inc. (Lexington, MA, USA)	FDA approved for biomedical use as implant material
	Sugar and a 4HB precursor	AmBio™	Shenzhen Ecomann Biotechnology Co. Ltd. (Guangdong, PR China)	FDA approved
	Glucose, corn steep liquor, and γ-butyrolactone	Medpha PHA™	Medpha (Beijing, PR China)	Focuses on producing PHA for medical applications
P(3HB-*co*-3HV)	Glucose and a 3HV precursor	ENMAT™	Tianan Biologic Materials Co. (Ningbo, PR China)	Food contact material
	Hydrolyzed cane sucrose and propionate	BIOCYCLE™	PHB Industrial S.A. (Serrana, Brazil)	
P(3HB-*co*-3HHx)	Oils derived from seeds of plants such as canola and soy	Nodax™	Danimer Scientific (Bainbridge, GA, USA)	FDA approved for food contact; technology originally from Proctor & Gamble (Cincinnati, USA)
	Vegetable oils	–	Kanegafuchi Chemical Industry Co. Ltd. (Kaneka) (Tokyo, Japan)	
	Waste cooking oil	Solon™	RWDC Industries Ltd. (Athens, GA, USA)	
	Crops and kitchen waste, seawater	Bluepha PHA™	Bluepha Co. Ltd. (Beijing, PR China)	

[†]FDA: Food and Drug Administration in the United States

These factors can be influenced by the bacteria strain and the substrate used for PHA synthesis, together with the fermentation conditions [22, 68]. For example, P(3HB) has a high crystallinity (60–80%) [70], is very rigid (tensile strength of ~43 MPa) with a low elongation at break [71], and exhibits poor processing performance due to its rapid thermal degradation [52]. P(4HB) is another representative member of scl-PHAs with very different physicochemical and thermal properties. P(4HB) is a ductile material with an elongation at break attaining 1000%, which makes it the most elastic PHA homopolymer produced to date [72].

Different properties are expected for mcl-PHAs compared to scl-PHAs. The glass transition temperature (T_g) of PHAs is affected by the number of side-chain carbon atoms and tends to be lower for mcl-PHAs [61, 69]. As the T_g of mcl-PHA is often lower than the room temperature, this may lead to elastomeric properties within appropriate temperature ranges [72]. Overall, mcl-PHAs have a low crystallinity, are elastic and flexible, and exhibit high elongation at break and moderate tensile strength. These PHAs also have lower T_m ranges compared to scl-PHAs [42, 69].

PHA copolymers of varying compositions, molecular weights, and architectures have been synthesized by many studies [71, 73–75]. Our broadened knowledge of PHAs has enabled the development of new materials with unique properties. Copolymerization has provided the opportunity to control the stereochemical microstructure of PHAs while enabling to modulate their physicochemical and thermal properties. These copolymers can be tailored for specific applications via a proper balance between the mechanical and thermal properties, together with the degradation rate [62]. For example, the low temperature threshold between the T_m and the onset of thermal degradation in P(3HB) causes its poor thermal stability during processing [72]. To address this shortcoming, the introduction of other monomeric units into the backbone of P(3HB) has led to a lower T_m while increasing its elongation at break and reducing stiffness [62].

Among the currently identified PHAs, the scl-PHA polymers that have 3HB as their main backbone monomer often show high crystallinity (e.g., 60–80%), stiffness, and brittleness, depending on the monomer composition and the mole fraction of the monomer [68]. These scl-PHAs include P(3HB), P(3HB-*co*-4HB), P(3HB-*co*-3HV), and poly(3-hydroxybutyrate-*co*-3-hydroxypropionate) [P(3HB-*co*-3HP)]. In comparison, the mcl-PHA polymers mainly composed of 3-hydroxyhexanoate (3HHx) and 3-hydroxyoctanoate (3HO) show elastomeric properties, with high elongation at break and tensile strength, low crystallinity and low T_m [68]. The ratio of the scl-PHA to mcl-PHA in a copolymer affects the final tensile strength and elasticity [19].

Material properties of some PHAs with different monomer compositions have been compared with those of polypropylene in Table 2 [9, 14, 19, 52, 61, 68, 69, 72, 76]. The following sub-sections briefly summarize the properties of P(3HB) and P(4HB), and some of their most-studied copolymers.

P(3HB)

P(3HB) has a slow crystallization rate, a low biodegradability rate compared to other PHA polymers, and a melting temperature (T_m) too close to its degradation temperature, which leads to a very narrow melt processing window [9]. The T_m and the thermal degradation temperature of P(3HB) are 170–180 °C and 180–190 °C, respectively [52], and its T_g is in the range of 0–5 °C [69]. The T_m of P(3HB) varies depending on the carbon source used in its production [69]. There have been reports of alterations in the molecular weight of P(3HB), as well as the generation of crotonic acid, when the processing temperature exceeds 170 °C [69, 77]. After maintaining at 190 °C for 1 h, P(3HB) has been found to lose almost half of its original molecular weight [69, 78].

The products made of P(3HB) often have low mechanical strength and are susceptible to physical aging [79]. The high crystallinity of P(3HB) makes it brittle and reduces its elongation at break. Nevertheless, P(3HB) outperforms many competing fossil-based plastics when it comes to its resistance against ultraviolet (UV) waves [9]. Furthermore, P(3HB) is one of the polymers that do not change their properties over a broad range of temperatures when stored for several years. This beneficial characteristic can particularly be of interest for the production of hard/creep-resistant

Table 2 Comparison of the properties of polypropylene to those of P(3HB) and P(4HB), as well as the commonly reported properties of several PHA copolymers at a moderate range of comonomer composition. Adopted from [9, 14, 19, 52, 61, 68, 69, 72, 76]

Property	Polypropylene	P(3HB)	P(4HB)	P(3HB-*co*-4HB)	P(3HB-*co*-3HV)	P(3HB-*co*-3HHx)
Tensile strength (MPa)	38	36–43	50	4–40	20–38	5–20
Young's modulus (GPa)	1.7	2.5–3.5	0.07–0.15	4–34	1–5	5–940
Elongation at break (%)	400	3–7	1000	10–80	20–50	10–850
Melting temperature (°C)	176	170–180	60	158–170	130–170	127–170
Glass transition temperature (°C)	−10	0–5	−51	−18 to 0	−7 to 5	−12 to 2

items. Another desirable feature of P(3HB) is the flexibility of adapting its melt viscosity to different processing techniques [9].

Mechanical characteristics of P(3HB) are comparable to those of isotactic polypropylene. This includes the tensile strength (36–43 MPa *vs.* 38 MPa, respectively) and Young's modulus (2.5–3.5 GPa vs. 1.7 GPa, respectively) (see Table 2). However, the elongation at break for P(3HB) is significantly lower compared to polypropylene (3–7% vs. 400%, respectively) [69]. As for the crystal structure, P(3HB) grows into extremely thin lamellar crystals that can arrange as spherulites, if produced from the melt, or turn into oblong lath-like single crystals in dilute solutions. The lamellar thickness of P(3HB) spherulites are often around 5 nm in size, although the length scale can be considerably lower when the crystals are produced from solutions [69, 77, 80].

P(4HB) and P(3HB-*co*-4HB)

A recent comprehensive review of P(4HB) covers the main aspects of its chemical and biological synthesis, material properties, biocompatibility and biodegradability, as well as the monomer composition and microstructure control of P(3HB-*co*-4HB) copolymers [76]. P(4HB) is a thermoplastic polymer with a T_m of 60 °C and a T_g of −51 °C [76]. When heated to up to 200 °C, P(4HB) is reasonably stable and exhibits only a moderate molecular mass loss [81]. Furthermore, P(4HB) is substantially more flexible than most synthetic resorbable polymers such as poly(L-lactic acid) (PLLA) and poly(glycolic acid) (PGA) [76]. This is a consequence of a more flexible backbone comprised of trimethylene and ester units and without pendant methyl groups.

In particular, P(4HB) has a remarkable elongation at break (~1000%) [9, 76]. This greatly exceeds that of polymers such as P(3HB), poly(lactic acid) (PLA), or PGA, which have elongations at break of only 1.5–20% [9, 69, 82], and is even superior to that of polycaprolactone (PCL), with an elongation at break of 60–800% [9, 82, 83]. Oriented P(4HB) fibers can attain a high tensile strength (545 MPa) [9], which exceeds that of polypropylene (PP) sutures (410–460 MPa) [9]. When P(4HB) is stretched, its mechanical strength increases while the material maintains its flexibility. This is unlike PLLA or PGA that exhibit a rise in their mechanical strength but become brittle in the process [17, 76].

Doi et al. [84], in 1988, originally reported on the production of a new copolyester of 3HB and 4HB [P(3HB-*co*-4HB)] by *Alcaligenes eutrophus* via a nitrogen-free culture of 4-hydroxybutyric acid or 4-chlorobutyric acid. Using butyric acid alone as a carbon source led to the accumulation of P(3HB) homopolymer. Compared to the T_m of ~179 °C for P(3HB), no noticeable decrease in the T_m was observed

with increasing fractions of 4HB units. However, an increase in 4HB fractions reduced the enthalpies of fusion (i.e., reduced crystallinity), which eventually approached zero at 49 mol % 4HB. The study revealed that the sequence distributions of 3HB and 4HB units in the produced copolymer were close to a statistically random distribution, which indicated the production of a completely amorphous copolymer [84]. In 2001, Metabolix Inc. patented a genetically modified and stable organisms (e.g., *Escherichia coli*), producing P(4HB) and its copolymers from inexpensive carbon sources. The patent is currently held by Tepha, Inc. [76], which was recently acquired by Becton, Dickinson and Company (BD) [85].

P(3HB-*co*-4HB) copolymers can range from being thermoplastic to fully elastomeric depending on the fraction of 4HB in the structure [9, 76]. For example, (3HB-*co*-4HB) copolymers with a 4HB fraction of 20–35% are elastomeric, which can extend with applying force and return to their original state upon removing the force [76, 81]. The remarkable material characteristics of (3HB-*co*-4HB) are considerably different from other scl-PHAs such as P(3HB) and P(3HB-*co*-3HV) [9]. Increasing the mole fraction of 4HB in (3HB-*co*-4HB) copolymers increases the elongation at break [68]. For example, the incorporation of up to 34 mol% 4HB units [7] can improve the elongation at break and impact strength, but at the cost of reduced modulus and tensile strength [86].

P(3HB-*co*-3HV)

Biopol™ is the trade name of a P(3HB-*co*-3HV) copolymer that was produced by Monsanto. This copolymer was later offered under the trade name Mirel™ in the context of a joint venture between a company formerly known as Metabolix, Inc. and Archer Daniels Midland (ADM) [9]. P(3HB-*co*-3HV) has a variety of application in packaging, shampoo containers, disposable cutlery, cups, as well as in medical patches and surgical pins [62, 87]. P(3HB-*co*-3HV) copolymers have a lower T_m compared to P(3HB), enabling an expanded range of processing temperatures. Analyzing the properties of this copolymer upon increasing the 3HV content has indicated a gradual decrease in T_m [68], which can vary between 75 and 170 °C depending on the percentage of 3HV moiety in the copolyester [14]. Nevertheless, incorporating small amounts of 3HV units is not sufficient to bring down the T_m of P(3HB-*co*-3HV) much below 150 °C [44]. In 1992, a commercially produced P(3HB-*co*-3HV) by Imperial Chemical Industry Biological (ICI) showed that with increasing the 3HV content from 10 to 20 mol%, the T_m could drop to 140 °C and 130 °C, respectively [9].

The thermomechanical properties of P(3HB-*co*-3HV) copolymers can exhibit considerable variations depending on the percentage of 3HV. Studies have shown that

P(3HB-*co*-3HV) often exhibits a relatively high degree of crystallinity in a broad range of compositions (from 0 to 95 mol% 3HV) [62, 88]. The incorporation of 3HV comonomer units has a limited effect on reducing the excessive crystallinity of PHA, which is due to the isodimorphism phenomenon [89]. The 3HV units are readily included in the crystal lattice of 3HB units and vice versa, and do not contribute to the anticipated disruption of crystallinity [90]. Upon increasing the 3HV content from 10 to 20 mol% for the ICI grade of P(3HB-*co*-3HV), the study in 1992 showed a decrease in crystallinity from 60 to 35% [9].

When compared to P(3HB), a lower stiffness and Young's modulus, a higher elongation at break, and improved flexibility and ductility are expected for P(3HB-*co*-3HV) [13, 68]. The Young's modulus of the copolymer is approximately between 1–5 GPa [91]. The flexural modulus and impact strength of P(3HB-*co*-3HV) copolymers can also be regulated by the content of 3HV units [84]. Furthermore, the toughness and flexibility of P(3HB-*co*-3HV) improve with increasing its 3HV content [92, 93]. For the two P(3HB-*co*-3HV) ICI grades studied in 1992, a tensile strength of 25 and 20 MPa, a flexural modulus of 1.2, and 0.8 GPa, and an elongation at break of 20 and 50% were reported after increasing the 3HV content from 10 to 20 mol% [9].

These characteristics make P(3HB-*co*-3HV) a useful material for producing films and fibers with different elasticities [62]. Additional improvements in the thermomechanical properties of P(3HB-*co*-3HV) can be achieved by grafting or compounding with other polymers [14]. When compared to P(3HB), the presence of 3HV moieties in P(3HB-*co*-3HV) can enhance the oxygen barrier characteristics and enable a higher viscosity in a molten state, which could be beneficial in extrusion processes [91]. Good gas barrier properties can particularly be useful in the production of biodegradable food packaging material, as it could enable an extend shelf life of food and reduce food waste [62]. The gas barrier properties of P(3HB-*co*-3HV) can be further improved by various strategies such as melt blending with other polymers [14, 94] and using multilayer design strategies [8, 95]. While multilayer approaches have a great potential to generate products with optimal properties, the effects of different combinations of layers, compositions, and their production technologies need further investigation [95].

P(3HB-*co*-3HHx), P(3HB-*co*-3HO), and P(3HB-*co*-3HD)

In the late 1980s, the researchers at Procter & Gamble (Cincinnati, OH, USA) initiated the early development of this class of PHA copolymers. Then, in 1994, Shiotani and Kobayashi (scientists from Kaneka in Japan) reported the discovery of microorganisms capable of producing P(3HB-*co*-3HHx) copolymers and patented their finding [44, 96]. This was a surprising scientific breakthrough

because, at the time, it was widely accepted that microbes produce either scl-PHAs or mcl-PHAs, depending on the type of active PHA synthase in the production strain [9]. Noda and coworkers originally developed and patented the hybrid copolymers of scl-PHA and mcl-PHA, consisting of 3HB and small amounts of different mcl-PHA comonomer units (i.e., 3HHx, 3HO, 3HD) [9, 44, 90].

Unlike the 3HV units in P(3HB-*co*-3HV), which are readily incorporated into the crystal lattice of 3HB units and vice versa (isodimorphism) [89, 90], the side chains containing more than three carbon atoms cannot enter into the crystal lattice structure of P(3HB). Thus, mcl-PHA comonomer units such as 3HHx, 3HO, and 3HD (rejected from the crystal structure) are randomly incorporated into the copolymer as an effective way of disrupting the excessive regularity of P(3HB) homopolymer [44]. This has enabled a significant reduction in the crystallinity, accomplished by adjusting the level of appropriate mcl-PHA comonomer units (featuring a side chain of three or more carbon atoms), which are distributed within the dominant 3HB comonomer units [44, 97]. This technology is currently available under the commercial brand name of Nodax™ [44, 90].

Interestingly, the efficacy of 3HHx, 3HO, and 3HD comonomers in lowering the T_m is essentially the same for a given mole percentage of the incorporated comonomer. Therefore, any of these mcl-PHAs are capable of effectively disrupting the regular structure of P(3HB), as long as the side group contains at least three carbon atoms [44]. The mcl-PHA units in Nodax™ copolymers can disrupt the 3HB matrix in a more efficient manner than the achiral 4HB building block does in P(3HB-*co*-4HB). In particular, P(3HB-*co*-3HHx) copolymers containing 10–17 mol% of 3HHx can provide remarkable flexibility, as evidenced by their high elongation at break (up to 850%), which is superior to the performance of commercially available P(3HB-*co*-3HV) containing 20 mol% 3HV [9, 98].

P(3HB-*co*-3HHx) copolymers offer excellent elasticity and tensile strength. Increasing the mol% of 3HHx makes the properties of the copolymer more similar to elastomers and expands the application of PHAs [68]. Other mechanical properties of P(3HB-*co*-3HHx), such as hardness and rigidity, can be adjusted depending on the percentage of 3HHx units [99, 100]. For example, a P(3HB-*co*-3HHx) copolymer containing 5.9 mol% 3HHx was reported to have an elongation at break of 163%. In another study, when the mol% of 3HHx units was only 2.5%, a tensile strength of ~26 MPa and a Young's modulus of ~631 MPa was reported [100, 101]. Blends of P(3HB) and P(3HB-*co*-3HHx) have also been used to achieve a broad range of elongation at break (15%-106%), while the tensile strength of the blends decreased by increasing the percentage of P(3HB-*co*-3HHx) from 40 to 60% [100].

Terpolymers and Multilayer PHAs

Designing PHA terpolymers might be a better alternative to copolymers. In a terpolymer, the properties of the material are enhanced by incorporating more than one secondary monomer into the polymer structure [33, 87, 102–104]. For example, a P(3HB-co-3HV-co-4HB) copolymer containing 3 mol% 3HV and 93 mol% 4HB has shown an elongation at break of 430%, a tensile strength of 14 MPa, and a Young's modulus of 127 MPa, whereas a terpolymer containing 34% 3HV and 55% 4HB has revealed a Young's Modulus of 618 MPa [102]. Similarly, a P(3HB-co-3HV-co-3HHx) copolymer has been reported to attain an elongation at break of 408%, a tensile strength of 12 MPa, and a Young's modulus of 258 MPa when 39 mol% 3HV and 3 mol% 3HHx are used, while showing a relatively low crystallinity due to the incorporation of both 3HV and 3HHx comonomers [103]. Another study investigated a terpolymer of P(3HB-co-3HV-co-3HHx) with ~68 mol% of 3HB, ~17 mol% of 3HV, and ~15 mol% of 3HHx. The terpolymer was obtained via the MMC technology, using fruit pulps as feedstock, and then mixed with P(3HB-co-3HV) [104]. It was found that the higher the 3HHx fraction in P(3HB-co-3HV-co-3HHx), the higher the increase in flexibility [104]. This could be attributed to the interference of 3HHx with the crystallization process [105]. Hence, the mechanical response can change from a rigid/fragile to a more ductile behavior after blending P(3HB-co-3HV) with P(3HB-co-3HV-co-3HHx) [104, 105].

Adopting a multilayer approach can also contribute to improving the mechanical and gas barrier properties [95]. Multilayer assembly of biodegradable polymers may allow the creation of multifunctional packaging materials with unique barrier and mechanical properties through more convenient and cost-effective techniques than some functionalization methods such as copolymerization [106]. In a multilayer approach, some layers are meant to provide adequate mechanical resistance, while others may serve as gas and moisture barriers [107]. In general, the outer layers may provide good water resistance and mechanical strength, and the inner layers are designed to enhance the gas barrier properties [95].

Biodegradability of PHAs

Biodegradation is the process in which organic materials undergo decomposition by microorganisms, or enzymatic/non-enzymatic hydrolysis via biochemical reactions (aerobically or anaerobically) [76]. The structure and properties of a polymer as well as the location, weather, and climatic conditions may have a significant influence on its biodegradation rates. A complete breakdown of a biodegradable material might involve microorganisms such as bacteria, archaea, fungi, and algae [108]. Most biodegradable polymers (e.g., PLA, PCL) degrade only in a narrow set of environmental conditions, whereas PHAs are degradable in a wide range of managed and unmanaged environmental conditions [109]. PHAs are degraded by surface erosion via chemical hydrolysis or by enzymatic interactions [76, 81]. It has been reported that the crystallinity index of PHAs does not change with biodegradation [108, 110], which is consistent with a surface erosion mechanism [108].

Composting is one of the most-studied forms of biodegradation (ASTM D5338-15R21 and ISO 14855-2:2018). Labeling standards are often used to define whether something is compostable (ASTM D6400-23) [31]. The certification committee, TÜV AUSTRIA, makes a distinction between the certification for degradability in industrial composts, home composts, as well as in soil, marine water, and fresh water (TÜV Austria, 2022) [46]. During the industrial composting, biodegradable materials are exposed to oxygen inputs and temperatures higher than that of soil biodegradation, and the environment is controlled in terms of moisture content, carbon-to-nitrogen ratio, etc. [31, 111]. Compostable packaging is one of the potential solutions to prevent waste, to circulate materials, and to regenerate nature [111], alongside strategies like biotechnological upcycling [112]. Nevertheless, industrial composting is an energy-intensive process that takes several weeks and might have its own environmental impacts [111].

A material that undergoes incomplete biodegradation and does not meet the standards of compostability could lead to the formation of microplastics in the environment [113]. A large portion of the plastics waste exists as microplastics (defined as smaller than 5 mm in size) [114], which is now recognized as a major pollutant of concern in the environment [115]. It is estimated that annually over 40 million tons of plastics will enter the environment, of which approximately 11 million tons will be in the form of macro- and microplastic debris that might end up in the ocean [69, 116]. A number of studies have looked into blending polyolefins with biodegradable polymers (e.g., starch, proteins, natural fibers) to increase their susceptibility to biodegradation [117]. Nevertheless, it is an open question whether such blends could decompose into adequately small particles, or merely fragmented into microplastics [5]. In contrast, small-sized PHA particles in nature undergo biodegradation and do not leave behind any remnants and therefore, are not resistant in their environment. Thus, there should be no concerns about "secondary microplastics" as it does not happen in the case of PHA biopolymers. This follows the first principle of Green Chemistry, with regard to avoiding the generation of precarious waste [41].

In contrast to fossil-based plastics, PHAs can fully degrade by microorganisms at a fast rate under aerobic and anaerobic conditions (i.e., home compost, industrial

compost, soil, seawater, landfill). Hence, PHAs are considered to be biodegradable materials as defined in accordance with international standards [118, 119], which require plastics to exhibit significant changes in their chemical structure upon exposure to naturally occurring microorganisms [120, 121]. The biodegradation of PHAs depends on a number of environmental factors, such as pH, temperature, humidity, oxygen, as well as the population of microorganisms and availability of nutrients in the environment [120].

Apart from environmental factors, the properties of a biopolymer, such as its monomeric composition, crystallinity, lamellar thickness, molecular weight, surface area, and additives also influence the biodegradation process. With an increase in the chain length, the crystallinity of biopolymers can decrease, which enhances their biodegradability [100]. A key element of PHAs hydrolysis is the chiral center of the PHA monomer in the R configuration, which is recognized by enzymes designated PHA depolymerases [76, 122]. Under different natural environments, microorganisms can degrade PHA into low molecular weight oligomers or monomers by secreting PHA depolymerase. These oligomeric and monomeric components are then taken up by the cells as nutrients [72].

Given the biological origin and biodegradability of PHAs, these materials have recently drawn attention as one of the ideal bioplastics to reduce the negative impact of microplastics in the environment and to serve as alternatives to conventional plastics [69]. Biodegradation of PHAs under a variety of natural environments has been the subject of many studies in the last three decades [120], including a recent meta study in the marine environment [108] and a comprehensive review paper [31].

Biomedical and Pharmaceutical Applications

Biocompatibility of PHAs

Biomass-based materials have recently gained great interest in the health sector, given the emerging interdisciplinary research in bioengineering and medicine [21]. PHAs can exhibit similar properties to fossil-based polymers, including high T_m and high tensile strength [100] while being an eco-friendly alternative. In particular, Gram-positive species used for PHA production offer another major advantage by eliminating the immunogenic lipopolysaccharides [123], which are the main source of impurities in PHAs produced by Gram-negative bacteria. These lipopolysaccharides have been reported to induce strong immunogenic reactions [55]. Biocompatibility and biodegradability of PHAs, as well as their piezoelectric properties, make PHAs an attractive biopolymer for biomedical applications [100]. The

biocompatibility and biodegradability of PHAs have made them the focus of a high number of research studies [72].

The polymeric biomaterials used for clinical applications are generally meant to be implanted into host tissues in the body. These biomaterials should not elicit any negative response at the implantation site, which differentiates them from general-purpose polymers [100, 124]. It has been reported that PHAs do not induce any thrombosis or antigenic response even after being in contact with blood in the human body during long-term use [100]. The biocompatibility of PHAs is a key factor in the rapid growth and proliferation of tissues onto and within these materials. Therefore, PHAs used in the biomedical field should be devoid of harmful substances and possess high purity [100]. The biocompatibility of PHAs originates from their monomeric units, which also naturally exist in the human body. For instance, in P(3HB), the monomeric unit is 3HB, which is a normal metabolite found in human blood [100, 125], and is produced in the human liver via the oxidation of fatty acids [72, 126]. PHAs can be synthesized to exhibit high molecular weights, as high as several millions of g/mol, with low polydispersity [76, 127].

PHAs can exhibit properties characteristic of thermoplastic and elastomeric materials [76]. For example, while scl-PHAs may have properties comparable to polyethylene or polypropylene, the properties of mcl-PHAs may resemble those of elastomers and rubbers [23, 43]. The wide range of monomer make-up can also offer a variety of physical properties making them suitable for value-added pharmaceutical and medical applications. Thus, one of the fastest-growing fields for PHA materials is their biomedical applications [76]. PHAs are considered potential materials for use in temporary implants, therapeutic devices, controlled drug delivery systems, and three-dimensional (3D) scaffolds for tissue engineering applications [105, 128–131]. PHAs have also been used as surgical sutures [132, 133], in wound dressings [73, 134], tissue-engineered blood vessels [135] and heart valves [136], nerve conduits [137], and as ligament and tendon [126], bone [138, 139] and cartilage/osteochondral scaffolds [72, 140, 141]. PHAs have also been shown to support the growth of, fibroblasts, chondrocytes, and epithelial cells under in vitro environments [72, 142, 143]. Some other reported applications of PHAs include tooth filling and fixation materials for bone fractures [144].

The immunological and physiological responses upon PHAs degradation indicate their biocompatibility, as a series of studies have reported that PHAs can promote cell adhesion and proliferation and do not trigger a robust in vivo immune response when implanted in rats, rabbits, and humans [72, 126, 139]. Furthermore, the piezoelectric characteristics of PHAs make these materials a candidate for the repair of damaged nerves. Improved nerve regeneration in

rats has been reported, hence suggesting PHA as a potential alternative to the conventional nerve graft materials [145].

The following sections provide an overview of PHA materials used in medicine. In particular, it aims to compare PHAs with other biodegradable materials used in biomedical applications (Table 3) [15, 68, 76, 82, 146, 147]. Typical representatives of the biomaterials used in medicine are PLA, PGA, and PCL, which have been approved by the US Food and Drug Administration (FDA) for use in various biomedical applications [76, 148, 149]. One of the major shortcomings of PLA is its degradation by burst-release that causes the accumulation of large amounts of lactic acid and leads to acidic pH after being implanted in the host [72, 76]. In contrast, PHAs maintain the pH stability during the degradation process, which contribute to their widely reported biocompatibility [72]. The hydrolytic attack to PHA ester bonds is less prone compared to PGA and PLA, and therefore, the hydrolysis rate of PHAs is generally slower [76, 150].

Selected PHA Biopolymers

P(3HB)

P(3HB) used in medical applications require the end product to be highly pure, free of halogenated solvents, toxins or other residual impurities from its manufacturing process [51]. The extraction process of PHAs affects their purity and is crucial in polymer recovery, while also influence the major characteristics of these biopolymers for their intended applications. For example, the molecular mass, degree of crystallinity and monomeric composition of the polymer are known to be significantly affected by the extraction process [55]. After successful extraction of the biopolymer from the cell biomass, purification of the extracted PHA is necessary to eliminate impurities (e.g., bacteria, solvents, color). This enables the use of these biopolymers in sensitive areas, including in the medical industry [55].

Diverse applications of P(3HB)-based biopolymers include plates, membranes, and 3D scaffolds for tissue engineering. These applications extend to the development of new drug dosage systems where micro- and nanoparticles made of P(3HB) are used to encapsulate a wide range of pharmacological drugs [151, 152]. P(3HB) biopolymer is also known to be a useful biomaterial in cancer detection. The breast cancer cells (T47D) have been shown to have a stronger attachment to P(3HB), extracted from *P. plecoglossicida*, in comparison to normal epithelial cells [153]. This biocompatibility with mammalian cells is a characteristic that has allowed the application of PHAs, particularly P(3HB), in surgical tools, wound dressings, bone repair, and drug delivery applications [55, 154].

P(3HB) offers slow biodegradation, low toxicity, and good biocompatibility without causing severe inflammatory responses. Under in vivo environments, P(3HB) degrades to 3HB, which is a common metabolite in all higher living beings [151, 155]. Hence, the use of P(3HB) in various potential medical devices with desirable outcomes has been demonstrated [151]. It is known that 3HB at concentrations of 30–100 mg/L is naturally present in human blood [72] and can promote tissue regeneration and reduce inflammation [53]. Furthermore, 3HB can act as a source of energy for the body when needed (e.g., starvation) and is eventually excreted as carbon dioxide [72].

P(4HB) and P(3HB-*co*-4HB)

The FDA approved P(4HB) for its use as a resorbable monofilament suture in 2007 [76, 156] and as a suture material in general soft tissue approximation and/or ligation [156]. After the FDA approval of P(4HB) sutures, it became the first long-term resorbable implant that entered the market in many years [17, 76]. In recent years, there has been a substantial increase in its use in clinical settings [100]. The biodegradation product of P(4HB) is 4HB, which is a compound that normally exists in the human body and is biocompatible [76]. P(4HB) has been used in biomedical devices for soft tissue repair thanks to its low crystallinity, high flexibility, ductility, and ease of processing, when compared to P(3HB) [18, 157].

Certain characteristics of P(4HB) make it stand out among not only PHA materials but also in comparison

Table 3 Comparison of the properties of P(3HB) and P(4HB) and those of some synthetic biodegradable polymers. Adopted from references [15, 68, 76, 82, 146, 147]

Property	P(3HB)	P(4HB)	PGA	PLA	PLLA	PDLLA[†]	PCL
Tensile strength (MPa)	36–43	50	60–100	21–60	15–150	28–50	16–42
Young's modulus (GPa)	2.5–3.5	0.07–0.15	6–7	0.35–3.5	1.2–4	1–3.5	0.2–0.4
Elongation at break (%)	3–7	1000	1.5–20	2.5–6	3–10	2–10	60–800
Melting temperature (°C)	174–180	60	220–233	150–162	170–200	Amorphous	57–65
Glass transition temperature (°C)	0–5	−51	35–45	45–60	55–65	50–60	(−65)–(−58)

[†]PDLLA: poly(D,L-lactic acid)

with other polymers conventionally used for medical applications. P(4HB) has the strength of conventional suturing materials while being much more flexible [76]. As seen in Table 3, some properties of P(4HB) that make it a suitable polymer for medical applications include its highly stretchable and flexible characteristic, with a significantly high elongation at break of up to 1000% [76]. This level of ductility greatly exceeds that of other biodegradable polymers such as P(3HB), with an elongation at break of about 3–7% (Table 3). The tensile strength of oriented P(4HB) fibers has been reported to be about 545 MPa, which is higher than that of PP sutures (410–460 MPa) [9]. This makes P(4HB) a viable option for biological fiber applications (e.g., sutures), although the Young's modulus of P(4HB) sutures is significantly lower than some other marketed monofilament alternatives [9, 81].

One of the key properties required for the use of PHAs in tissue engineering is the rate of biodegradation. In tissue engineering, the general consensus is that the degradation rate of the scaffold should match the rate of tissue regeneration under both in vitro and in vivo conditions [100]. PHA copolymers with 4HB monomeric units, such as P(3HB-*co*-4HB), have a higher degradation rate than the copolymers with 3HB units (e.g., P(3HB-*co*-3HV) [11, 100]. Likewise, the biodegradation rate of PHA copolymers with 4HB units have been shown to be much greater than P(3HB) polymer or the copolymers containing 3HB [100, 158]. Thanks to its biocompatibility, P(4HB) has been used as a new and improved biomaterial in implants, wound care, as well as in tissue engineering scaffolds. This has enabled bridging the gap when a desired level of degradation is required under in vivo environment [76, 81, 156]. Nevertheless, the limited availability of P(4HB) from commercial sources is considered to be one of the factors hindering the widespread use of its remarkable potential in biomedical applications [76].

Some clinical P(4HB) products currently on the market include surgical meshes of knitted fibers and sutures. The P(4HB) homopolymer has been commercialized by Tepha Inc. (Cambridge, MA), recently acquired by Becton, Dickinson and Company (BD), which is based on a proprietary transgenic fermentation process using E. coli [9, 62]. This polymer has been characterized by a good resorption in vivo and remarkable flexibility, which makes it a desirable candidate for implantable medical applications [62]. For example, TephaFLEX™ [85] has been used in medical products including surgical meshes, sutures, surgical films, wound dressings, heart valves, and vascular grafts, among others [51, 59]. Other commercial brands of P(4HB) include GalaFLEX™ [159], BioFiber scaffolds [160], MonoMax® sutures [161], and Phantom™ Fiber sutures [162] (see Table 1) [17, 18]. Hence, P(4HB) stands out among PHA materials due to its high market value and large market potential [76].

P(3HB-*co*-4HB) copolymers have been attracting attention in the cosmetic industry and in the medical applications, including implants, anticancer drugs, and drug carriers that require non-toxicity, biodegradability, and biocompatibility [68, 163, 164]. Implantable rods prepared with P(3HB-*co*-4HB) have been used for the delivery of antibiotics such as Sulperazone®. It was reported that the release of the drug was controlled by the drug loading (drug/polymer ratio). The rate of drug dissolution was substantially higher than that of polymer degradation, indicating that the release of the drug was more dependent on drug dissolution than on polymer degradation [164].

P(3HB-*co*-3HV)

As stated earlier, P(3HB) homopolymer is more brittle than most synthetic fossil-based plastics. This brittleness can be reduced by the incorporation of 3HV monomers into P(3HB) chains while increasing its elasticity, flexibility, and toughness. The resulting copolymer becomes a suitable candidate for industrial and biomedical applications [1]. P(3HB-*co*-3HV) has been reported to be a valuable material for medical and pharmaceutical purposes [145]. In particular, P(3HB-*co*-3HV) has excellent properties such as low cytotoxicity, piezoelectricity, thermoplasticity, high crystallinity, resistance to ultraviolet radiation, and acceptable amounts of oils, fats, and alcohols [82]. Hence, the biocompatibility of P(3HB-*co*-3HV) has made it a promising material for biomedical applications.

The biocompatibility of PHAs has also been demonstrated in a study that made use of a melt-spun mixtures of P(3HB-*co*-3HV) and PLA [165]. These fibers produced by melt-spinning revealed a high tensile strength. Seeding human fibroblast cells on these fibers enabled to demonstrate their biocompatibility (via well-proliferated cells) as well as their biodegradability [165]. Given the substantial role of monomer composition in these copolymers, the biocompatibility and biodegradability of PHAs can be tuned to achieve the desired properties for biomedical applications [100]. When compared to other polymers used in biomedical applications (e.g., PLA), it has been shown that the biodegradation products of P(3HB-*co*-3HV) tend to be less bioactive under in vivo environments and leads to less tissue acidification. Furthermore, the rate of in vivo degradation for P(3HB-*co*-3HV) is lower than that of PLA, which makes this copolymer a desirable implantable material for bone regeneration and repair [166].

In vitro proliferation of various human cells has been achieved using P(3HB-*co*-3HV) as a support matrix. The same adhesion to P(3HB) and P(3HB-*co*-3HV) matrices were reported using various cell types, namely endothelium cells, hepatocytes, and fibroblasts [145]. Micro- and nanospheres made of PHAs can also serve as drug delivery

carriers. In these applications, the outer shell polymeric coating starts to degrade and enable the gradual release of incorporated drugs. For example, rods of P(3HB-*co*-3HV) have been loaded with a combination drug (cefoperazone/sulbactam) with the goal of in vivo implantation for the treatment of chronic osteomyelitis [145].

P(3HB-*co*-3HHx)

The 3D scaffolds used in tissue engineering have been one of the major applications of PHA biopolymers. For example, P(3HB-*co*-3HHx), dissolved in a solvent (e.g., chloroform) generates a homogeneous solution that can be processed via computer-aided additive manufacturing. The 3D scaffolds composed of wet-spun P(3HB-*co*-3HHx) fibers can offer enhanced compressive mechanical properties and have demonstrated good cytocompatibility, as evidenced by their ability to sustain the proliferation and differentiation of murine pre-osteoblasts toward an osteoblastic phenotype [167]. The biocompatibility of P(3HB-*co*-3HHx) for potential implantation in the human body has been studied, showing that these biopolymers reduce the adhesion of blood platelets and thrombogenicity when in contact with blood [100, 168].

In a study, using articular cartilage from rabbits, the scaffolds produced by a mixture of P(3HB) and P(3HB-*co*-3HHx) were shown to support the 3D growth of chondrocytes [100, 169]. Another study compared P(3HB-*co*-3HHx), P(3HB), and PLA materials after being subcutaneously implanted in rabbits for 6 months [170]. Overall, P(3HB-*co*-3HHx) elicited a very mild tissue response during the implantation period, unlike relatively acute immunological reactions observed for P(3HB) and PLA materials [170]. A similar study looked into the in vitro biocompatibility of P(3HB-*co*-3HHx), P(3HB), and PLA scaffolds [171]. After incubation for 10 days, the cells grown on P(3HB-*co*-3HHx) scaffolds were ~ 40% higher than that of P(3HB) scaffolds and ~ 60% higher than that of PLA scaffolds. The alkaline phosphatase (ALP) activity of the cells grown on P(3HB-*co*-3HHx) scaffolds was 50% higher than those of P(3HB) and PLA [171]. Hence, the presence of the 3HHx comonomer makes it possible to produce copolymer compositions with properties that can be tailored to specific applications [172].

The role of topographic morphology of P(3HB-*co*-3HHx) membranes on tissue growth has also been studied [173]. Membranes produced by solvent-casting, electrospinning, and compression-molding were used to investigate the in vitro adhesion, proliferation, and differentiation of human mesenchymal stem cells (MSCs). The results indicated the potential of these materials for guided tissue regeneration and co-culturing of cells with desired orientation (e.g., nerve, muscle and ligament cells), indicating that MSCs grown on the electrospun fibrous meshes can exhibit a specific orientation [18].

Previous studies have shown that P(3HB-*co*-3HHx) can also be a potential candidate for peripheral nerve tissue engineering [174, 175]. In a study, P(3HB-*co*-3HHx) scaffolds seeded with human bone marrow mesenchymal stem cells (hBMSC) showed a strong expression of three nerve marker genes [174]. Furthermore, the study investigated a terpolyester of 3HB, 3HV, and 3HHx [P(3HB-*co*-3HV-*co*-3HHx)]. The results indicated that the terpolyester films had stronger hBMSC adhesion, proliferation and differentiation when compared with those of P(3HB-*co*-3HHx) and PLA films. The scaffolds made of the terpolyester, with pore sizes of 30–60 μm, were reported to provide the most suitable environment for hBMSC cell proliferation and nerve differentiation.

PHA Beads

PHAs accumulate in the form of intracellular inclusions and are covered with a proteinaceous layer (i.e., granule-associated proteins or GAPs), which forms a network-like surface of polypeptides [176]. Thus, the intrinsic properties of PHA granules (Fig. 6a) make them an ideal candidate for the development of stable functionalized beads for biomedical applications, including for facilitating the production and purification of biologically active proteins [45]. The proteins identified on the surface of PHA granules have been classified into several major classes: (1) PHA synthases, (2) PHA depolymerases (PhaZ), (3) phasins (PhaP), (4) regulatory Proteins (PhaR, PhaF, PhaI), and (5) other GAPs (Fig. 6b [45, 177]). For example, phasins have been considered for applications in drug delivery systems, protein purification, and as biosurfactants [178–180]. Gaining additional knowledge about the structure, topology, and biochemical properties of GAPs can offer opportunities to rationally engineer these proteins and their functions while maintaining their ability to attach to PHA granules. Ultimately, this may lead to surface-functionalized PHA beads that could display desired protein functions, making them suitable for a broad range of applications in medicine.

Figure 6c shows some potential biomedical applications of PHAs [181]. Several review papers published in the past few years cover a wide range of biomedical and pharmaceutical applications for PHAs and for other bio-based materials [21, 72, 82, 100, 168, 172, 181–197]. Table 4 provides the main outlines of some of these review papers for additional reading.

Opportunities, Challenges, and Future Directions

Being bio-based materials, PHA bioplastics offer enormous opportunities for biomedical and pharmaceutical applications, while serving as a sustainable alternative to

Fig. 6 **a** A transmission electron microscopy (TEM) image of a bacterial cell showing PHA inclusions. Reproduced from Parlane et al. [45] with permission; **b** The structure of a PHA granule from *Ralstonia eutropha* and its surface proteins. Reproduced from Rehm [177] with permission; **c** Some biomedical applications of PHAs. Reproduced from Pulingam et al. [181] under the Creative Commons Attribution license
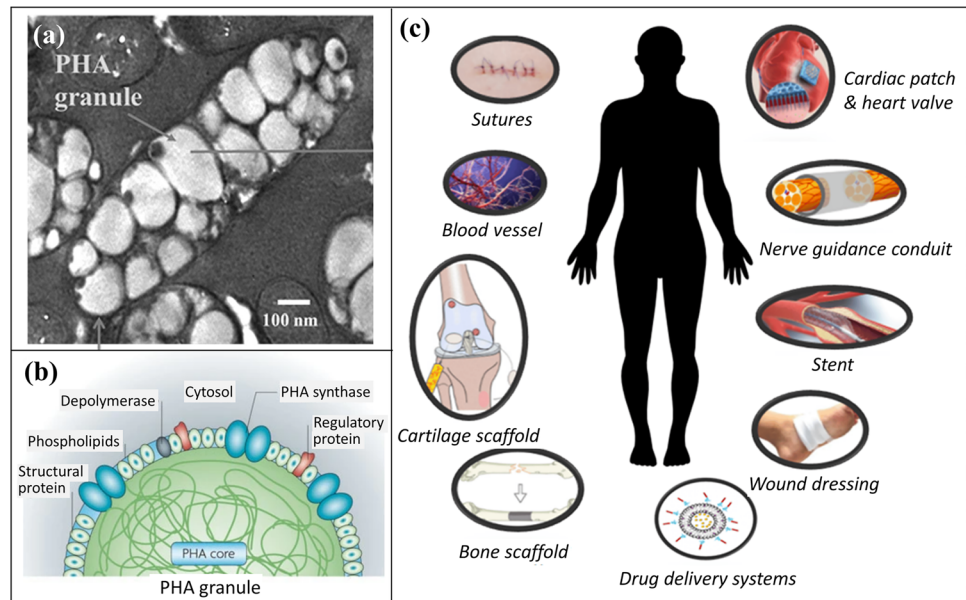
fossil-based packaging and single-use plastics. The biomedical field was estimated to be the second-largest market share for PHAs, in terms of volume, in 2022 [16]. In particular, the commercially available P(4HB) products have been used effectively in hernia repair, tendon and ligament repair, and for plastic and reconstructive surgery [17, 18, 182].

PHAs also present challenges and limitations that need to be addressed, including cost-effectiveness, processing challenges, and hurdles that affect their widespread availability. The production volumes of PHAs are small, and these materials are currently more expensive that the fossil-based plastics [198, 199]. Thus, targeting markets in which PHAs can introduce substantial advantages based on their unique properties could help PHAs gain additional market share. This includes the potential impact of PHAs on the CO_2 footprint compared to the current fossil-based materials [199]. Given some proven beneficial characteristics of PHAs, such as being non-toxic, biodegradable, and biocompatible, these polymers are ideal candidates for a broad range of functions as bioplastics, chemicals to serve as antibiotics, implant materials, and biofuels, among others [198, 200, 201].

Bioengineering technologies are progressively improving to tackle the high cost of producing bioplastics from bacteria [69]. Extensive research is being conducted to explore inexpensive substrates, such as carbon-based waste resources available via greenhouse gases (CH_4 and CO_2) and domestic/industrial wastewater plants [92, 115, 198, 202]. Commercial PHA producers are also exploring various other low-cost waste substrates for PHAs production, such as kitchen/food waste [50, 203], forest and agricultural wastes [204, 205], and shale gas in an effort to reduce production costs [10, 206]. For applications that do not require sterility, utilizing a mixed microbial culture (MMC) can produce PHAs at

high productivity and lower the costs. This is due to reduced requirements for control devices and, importantly, the MMC can utilize inexpensive feedstocks such as domestic or industrial effluents [10].

Organizations such as Go!PHA [207] have aimed at promoting PHAs as sustainable alternatives to the conventional fossil-based plastics and disseminating the benefits of PHAs to industries and consumers [56, 206]. Reducing the production costs while improving the mechanical properties of PHAs could open up additional market prospects and advanced applications [69]. Other potential strategies to achieve cost-competitive bioplastics are multilayer design strategies [8, 95] as well as new designs through the formulation of PHAs with additives, such as organic and inorganic fillers and fibers [2, 29], nucleating agents [208], chain extenders [112], plasticizers [209], and other functional additives [210–212], or via blending with other polymers (melt reactive blending and/or physical blending [27–29, 213–216], and specialized copolymers and composites [66, 217–223]. These strategies could lead to substantial improvements in mechanical properties, more flexible processability windows, and the thermal stability of the final product. Once compounded with other materials, the lower percentage of PHA in the final formulation can consequently reduce the materials cost [62].

Co-production of bio-based value-added products (VAPs) using waste substrates can also reduce the overall production costs (Fig. 7) [56]. The biorefinery strategy is a combined notion with numerous methods linked in series for the transformation of waste substrates to bio-based VAPs [56, 92, 224], while delivering more effective waste management systems, reducing waste disposal expenses, and eventually leading to economic sustainability and eco-friendly

Table 4 The outlines of some recently published review papers related to the applications of PHAs in biomedical fields

References	Publication Year	Main outlines of the paper
Li et al. [21]	2023	Source and composition of biomass-derived materials; Biomass-derived fiber materials for biomedical applications; 3D printing of biomass-derived fiber materials; Conclusion and outlook
Żur-Pińska et al. [75]	2023	PHAs' characteristics, types, properties, and production methods; Bioplastics in TE and biomedicine—PHAs as smart and biodegradable materials; 3D printing techniques used for PHAs in TE; Future prospects; Conclusions
Deeken et al. [182]	2023	Fully resorbable poly-4-hydroxybutyrate (P4HB) mesh for soft tissue repair and reconstruction: A scoping review was conducted within PubMed and included articles published through October 2022. A total of $n=79$ studies were identified ($n=12$ in vitro/bench; $n=14$ preclinical; $n=6$ commentaries; $n=50$ clinical)
Kalia et al. [185]	2023	Biopolymer-synthetic, biopolymer-inorganic composites; Biomedical applications: Tissue engineering, Drug carriers and delivery, Medical implants, Biocontrol agents; Perspectives; Conclusions
Rodríguez-Cendal et al. [189]	2023	Properties of polyhydroxyalkanoates; Poly(3-hydroxybutyrate-*co*-3-hydroxyvalerate); PHBV composites for drug delivery applications; PHBV composites for tissue engineering applications; Conclusions; Future perspectives
Pramanik [190]	2023	Microorganisms for PHA synthesis; Synthetic mechanism; PHAs extraction techniques; Biodegradation and biocompatibility; Polyhydroxyalkanoates (PHAs) as a primer in different composite; Biomedical application; Conclusion and future outlook
Ladhari et al. [191]	2023	Polyhydroxyalkanoate polymers; Applications of PHA-based materials; PBAT: poly(butylene Adipate-*co*-terephthalate) fabrication approaches of PHA-based materials with antibacterial functionality; Integration of PHA-based nanofibers with antibacterial agents; Perspectives; Conclusions
Diniz et al. [192]	2023	PHA synthesis; PHA in biotechnology: Scaffolds in fabric engineering; Drug carriers; Other applications in medicine; Conclusions
Das et al. [194]	2023	General conversion of monomer to polymer; Biopolymer and classification of biopolymers; Properties of biopolymers; Synthesis methods of biopolymers; Physical properties and geographical orientation of recent studied biopolymers; Characterization of biopolymers; Applications of biopolymers; Challenges and future perspectives; Conclusion
Guo et al. [72]	2022	Properties of PHA; Applications of PHA: Soft tissue engineering; Organ tissue engineering; Vascular tissue engineering; Hart-valve tissue engineering; Nerve conduit tissue engineering; Bone tissue engineering; Cartilage tissue engineering; Others; Prospects and conclusion
Behera et al. [100]	2022	Classification of polyhydroxyalkanoates (PHA); Biosynthesis of PHA; Properties of PHA; Production and genetic regulation of PHA in various microorganisms; Applications of PHA; Conclusion and future perspectives
Pulingam et al. [181]	2022	Common types of PHA used in tissue repair and engineering; Biomedical applications of PHA; Biodegradability of PHA used in the medical sector; Conclusions
Gregory et al. [184]	2022	PHAs – bacterially derived polymers; PHA-based biomedical prototype development; Soft tissue engineering; Hard tissue engineering; Drug delivery; In vivo studies; Concluding remarks
Naser et al. [82]	2021	Poly(lactic acid); Polyhydroxyalkanoates (PHAs): PHAs' synthesis, PHAs' physical and thermal properties, PHAs' mechanical properties, PHAs' permeability and migration, PHAs' degradation; Applications; Current challenges; Conclusions, future research and outlook
Kaniuk and Stachewicz [172]	2021	Polyhydroxyalkanoates: types of bacterial polymers; Properties of polyhydroxyalkanoate polymers; Degradation of PHA polymers; Biocompatibility of PHA polymers; Electrospinning of PHA polymers; Biomedical application of PHBV electrospun fibers; Application of other PHA polymers; Conclusions and future prospects
Li et al. [196]	2021	Material properties of PHAs; Biocompatibility and biodegradability of PHAs; Degradation products of PHAs and their biological functions; Synthetic biology and metabolic engineering strategies for PHA production; Non-teratogenicity and non-carcinogenicity of PHAs; Manufacturing technologies for scaffold fabrication in tissue engineering; PHAs and PHA-based scaffolds for BTE; Conclusion and future perspective
Chai et al. [193]	2020	Polyhydroxyalkanoates (PHAs); Synthesis of Poly(3-hydroxybutyrate-*co*-4-hydroxybutyrate) [P(3HB-*co*-4HB)]; Surface Functionalisation of P(3HB-*co*-4HB); Biomedical Applications of P(3HB-*co*-4HB); Challenges and Outlook
Grigore et al. [168]	2019	Classification and production of PHAs; Properties of PHAs; Medical applications: Neuronal regeneration, Heart valves, Drug delivery systems for cancer therapy; Conclusion and future perspectives

Table 4 (continued)

References	Publication Year	Main outlines of the paper
Butt et al. [187]	2018	Biodegradable polymers; PHA synthesis; Biosynthetic pathways; PHA biodegradation; Biomedical applications: Tri-leaflet heart valve, Cardiovascular tissues, Drug delivery system, Drug carriers, PHA nanoparticles based targeted drug delivery; Conclusion; Future perspective
Lim et al. [188]	2017	Emerging properties of PHAs as bone tissue engineering scaffolds; Fabrication techniques and 3D-printed PHA scaffolds; PHAs and their composites-based scaffolds in bone tissue engineering; Conclusion and future perspectives

approaches [56, 224]. This approach can reduce the costs associated with the fermentation, if the combined manufacturing of several co-products can be accomplished with high yields without adversely affecting the metabolic equilibrium of cell. Some research teams have recently tested several co-products using different microbial strains (natural or genetically modified) [56]. Examples of these co-products are PHA-based proteins, polysaccharides, pigments, and organic acids, together with generating bioelectricity and biohydrogen as a high-demand co-product (Fig. 7) [56].

Conclusions

PHA-based homopolymers and copolymers are promising candidates as sustainable materials for a circular economy. PHAs do not induce any thrombosis or antigenic response even after being in contact with blood in the human body during long-term use. The biocompatibility of PHAs is also a key factor in the rapid growth and proliferation of tissues onto and within these materials when served as tissue engineering scaffolds. In the ongoing effort to reduce plastic waste, PHAs could play a substantial role due to their inherent biodegradability free of microplastics, customizable properties, and versatile applications. Effective collaboration among researchers, industries, and policymakers is crucial to overcome the existing challenges and unlock the full potential of PHA-based materials. Collaborative research, continuous innovation, advanced processing techniques, new types of monomers, and deepening our understanding of PHAs biodegradation and physiochemical properties could pave the way for their widespread use and greater market share. Furthermore, biorefinery approaches could enable seamlessly integrating PHAs into existing recycling infrastructure, while introducing additional bio-based products to the market.

Fig. 7 A biorefinery approach for production of value-added products. Reproduced from Yadav et al. [56] with permission
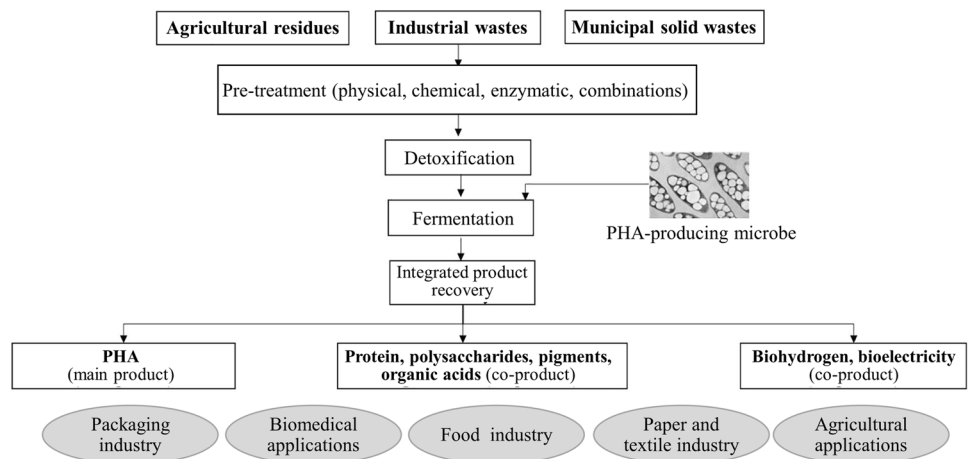
Declarations

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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