International Journal of Environmental Science and Technology (2023) 20:3409–3420
https://doi.org/10.1007/s13762-022-04213-9

REVIEW

Polyhydroxyalkanoates: a review of microbial production and technology application

A. A. Alves[1] · E. C. Siqueira[1] · M. P. S. Barros[1] · P. E. C. Silva[1] · L. M. Houllou[1]

Received: 12 January 2022 / Revised: 18 March 2022 / Accepted: 14 April 2022 / Published online: 7 May 2022

Abstract

Plastics of petrochemical origin are materials difficult to degrade, and they have caused environmental impacts. The development of new biotechnological strategies for the production of bioplastics has attracted the attention of researchers all over the world, enabling the production of economically more viable, biodegradable materials with different possibilities of application in various industrial sectors. The polyhydroxyalkanoates are biopolymers with physicochemical properties similar to those of polypropylene, polystyrene, and polyethylene commonly used by the industry. These bioplastics can be biosynthesized by various microorganisms and accumulate polyhydroxyalkanoates granules intracellularly. The high cost of polyhydroxyalkanoates production is still a limiting factor for its large-scale production, and the costs associated with the carbon source used are one of the reasons that increase the price of the product. This review discusses the main factors associated with polyhydroxyalkanoates production, providing an overview of the different attempts to produce the biopolymer from the use of low-cost substrates and the development of different fermentation strategies for the production of these polymers.

Keywords Bioplastics · Agro-industrial residues · Sustainability · Low cost

Introduction

Plastics of petrochemical origin are essential commodities in society, being widely used in a variety of products that provide comfort and quality of life to people. Due to their physicochemical properties, synthetic plastics have been an extremely relevant material from agriculture to the biomedical sector. However, its excessive use and its non-biodegradable composition generate major environmental problems, since the degradation rate of these materials is prolonged, with a half-life up to 500 years. In addition, plastics occupy large volumes in landfills, making it difficult for other organic materials to decompose (Vigneswari et al. 2021). In 2018, there was a disposal of approximately 396 million tons of plastic, with an estimate for the year 2050 of 810 million tons (Sharma et al. 2021).

Contamination by microplastics (plastics smaller than 5 mm) is also a frequent concern among researchers. These materials are present everywhere contaminating the soil, air, and the entire aquatic environment. Fish and other marine animals can consume the microplastics and affect the digestive process, leading to their death from malnutrition (Watteau et al. 2018). An alternative to replace traditional plastics and, consequently, reduce the problems caused by the inappropriate disposal of these polymers is the development of biodegradable materials. The polyhydroxyalkanoates (PHA) are highlighted as a class of polyesters biosynthesized by several microorganisms, when exposed to culture media with excess carbon and limitation of other nutrients such as nitrogen and magnesium. The bioplastics are produced intracellularly and accumulated in the form of hydrophobic granules of 0.2–0.5 µm, surrounded by a boundary layer of proteins (Albuquerque and Malafaia 2018).

This review explores the use of alternative carbon sources for the production of PHA by different groups of microorganisms, presenting an overview of the opportunities and challenges inherent in the sustainable production and economic viability of polyhydroxyalkanoates.

Editorial responsibility: Maryam Shabani.

E. C. Siqueira, M. P. S. Barros and P. E. C. Silva authors contributed equally to this article.

✉ A. A. Alves
andradealves@gmail.com

[1] Centro de Tecnologias Estratégicas Do Nordeste, Laboratório de Bioprocessos, Recife, Pernambuco, Brazil

Polyhydroxyalkanoates (PHA)

PHA is a class of biodegradable polyesters, consisting of hydroxyalkanoic acid monomers, produced by a wide variety of microorganisms (*Alcaligenes latus*, *Azobacter vinelandii, Bacillus megaterium, Cupriavidus necator*, *Pseudomonas oleovorans* e *Escherischia coli*) (Kumar et al. 2020). PHA biosynthesis happens when there is an excess of carbon and a limitation of essential nutrients for cell multiplication, such as phosphorus, nitrogen, and magnesium. Under these conditions, there is an accumulation of the biopolymer intracellularly in the form of granules as a source of carbon and energy reserve (Shahid et al. 2021). The versatility of its properties has made PHA widely applicable in biomedical devices, electronics, civil construction, automotive sector, packaging and agriculture, increasing its importance in the global market (Saratale et al. 2021; Bedade et al. 2021).

Polyhydroxyalkanoates were first reported by microbiologist Maurice Lemoigne in 1926, who observed PHA granules produced by *Bacillus megaterium* (Kumar et al. 2020). With the petroleum crisis, there was greater interest in research on the production of PHA. Researchers were attracted by the characteristics of the polymer such as resistance to UV radiation, biocompatibility, biodegradability, water insolubility, in addition to having a wide range of mechanical and thermal properties, making PHAs an excellent replacement for plastic of petrochemical origin (Bedade et al. 2021; Sharma et al. 2021).

The first PHA reported in the literature was polyhydroxybutyrate (PHB), a homopolymer that has four carbon atoms in its main chain, produced intracellularly by bacterium *Cupriavidus necator* (Saratale al. 2021). Among the more than three hundred species of PHA-producing microorganisms, the bacterium *C. necator* has been considered of great biotechnological interest due to its large-scale production capacity, accumulating up to 80% of its dry mass in PHB (Schmidt et al. 2016).

PHB is a thermoplastic polymer with a melting point around 180 °C capable of being molded and used in various industrial segments (Raza et al. 2018). The main limitation for its use is its high crystallinity (around 70%) and low elasticity, leaving the material fragile and brittle, requiring the addition of plasticizers, co-polymers, or modifying agents to minimize this limitation.

The mechanical properties of PHAs vary according to the number of carbon atoms that constitute the monomeric unit. The size of the carbon chain differentiates its mechanical characteristics, which can be rigid and fragile, for short-chain PHA (3 to 5 carbon atoms), up to more flexible and elastomeric polymers for medium-chain (6–14 carbon chains) and long (longer than 15 carbon chains) PHA. This difference in the chemical structure of the polymer is directly related to the species of microorganism, the carbon source used, and the growing conditions (Vigneswari et al. 2021; Bedade et al. 2021).

According to Shabina et al. (2015), there are about 150 types of hydroxyalkanoic acid monomers that are part of the chemical makeup of the polyhydroxyalkanoate family. These different chemical structures can be constituted by different functional groups such as halogens, epoxy, hydroxyls, carboxyls, enabling the formation of polymers with different properties (Chee et al. 2019). Figure 1 shows the general chemical structure of PHA.

Despite its excellent characteristics, PHA production is still limited due to its high production cost compared to synthetic plastics. The carbon sources used make production more expensive and can reach up to 40% of the total cost of the process (Carpine et al. 2020). Recent alternatives for sustainable PHA production involve the use of cheaper feedstock, and it includes agro-industrial by-products, as residual glycerol, agro-industrial residues, whey, vegetable oils from industrial processing/frying, and lignified biomass (Kumar et al. 2020; Saratale et al. 2021).

Bacterial mechanism for PHA biosynthesis

The understanding of the PHA synthesis pathway has been conducted since the 1920s. These pathways have already been elucidated, and some attempts to improve the efficiency of PHA biosynthesis have been made (Meng and Chen 2018). Recent advances are focused on systematic improvements in the biopolymer metabolic pathway, including changing the growth pattern for rapid proliferation, increasing cell size for greater PHA accumulation, and reprogramming biosynthetic pathways that redirect the metabolic flux (Chen and Jiang 2018; Meng and Chen 2018). Genome editing tools are being used for this purpose, such as CRISPR/Cas9 technology (Chen and Jiang 2018). In addition, the use

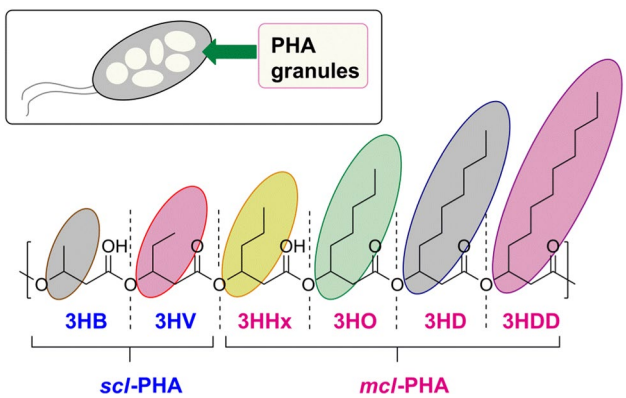

Fig. 1 General Chemical Structure of PHA (adapted from Bedade et al. 2021)

of non-traditional bacteria, such as halophytes (*Halomonas spp.*), is also being explored to minimize the complexity in PHA production (Ye and Chen 2021). Rapid bacterial growth on simple media and the possibility of achieving a high cell density with high PHA content are important factors for a successful production process. *E. coli* is a widely studied bacteria with well-established technologies for genome manipulation, cultivation, and processing; many studies focus on using *E. coli* to effectively produce these biopolymers (Meng and Chen 2018). This bacterium is not a PHA producer; however, genes involved in the biosynthesis of *C. necator* H16 have already been transferred into *E. coli*, and production can be observed in this microorganism (Slater et al. 1998). Since then, many genetic modifications have been tested to improve PHA storage at low cost with high productivity, either by producing various copolymers using metabolic engineering and/or synthetic biology strategies (Wang et al. 2014). The details of the PHA biosynthetic pathway and its related enzymes are extensively studied (Wang et al. 2014; Chen and Hajnal 2015). Many of these studies have been conducted to enhance the metabolic flux of PHA synthesis (Kourmentza et al. 2017; Tan et al. 2020; Bedade et al. 2021), such as the limitation of essential elements (nitrogen, phosphorus, sulfur, or iron); oxygen limitation; repression of the beta-oxidation cycle; over-expression of NADH (or NADPH); synthesis enzymes and construction of new pathways for synthesis of non-3-hydroxybutyrate (3HB) monomers, such as 4-hydroxybutyrate (4HB) or 3-hydroxyvalerate (3HV), from glucose as a substrate (Fig. 2). CRISPR/Cas9 technology, especially CRISPRi (interference CRISPR), has been successfully used to manipulate genes related to PHA synthesis (Tao and Chen 2017; Chen and Jiang 2018; Lin et al. 2021). CRISPRi-based genomic editing was used in repressing competing pathways in 4-hydroxybutyrate (4HB) production, allowing the glucose-generated flux to be directed exclusively to 4HB production (Chen and Jiang 2018). Tao and Chen (2017) used CRISPRi to repress the propionate competition pathway and direct only to 3HV formation. In another study, the CRISPRi was able to regulate the metabolic pathways related to PHBV synthesis, thereby enhancing PHBV production (Lin et al. 2021). The downregulation by CRISPRi on the citrate synthase genes (citZ and gltA) improved the PHBV accumulation by 76.4% (from 1.78 to 3.14 g/L). They also further shorten the PHBV fermentation period and enhance PHA productivity by 165%.

There are three main pathways for PHA synthesis in microbial systems, involving different substrate sources and forms of fermentation: pathway I, it involves the conversion of acetyl-CoA to 3-hydroxybutyryl-CoA; pathway II, the degradation of fatty acids by the β-oxidation mechanism; and pathway III, through fatty acid biosynthesis. Pathways I and III employ fermentable sugars, while pathway II uses fatty acids for microbiological growth and PHA production (Saratale et al. 2021). Figure 2 shows the representation of different metabolic pathways for PHA biosynthesis. The scl-PHAs are synthesized in three main steps, starting with acetyl-CoA, while mcl-PHAs can be synthesized in two different ways. The first route consists of the β-oxidation of fatty acids before their incorporation into the polyester chain; the second consists of fatty acid biosynthesis (Arumugam et al. 2019).

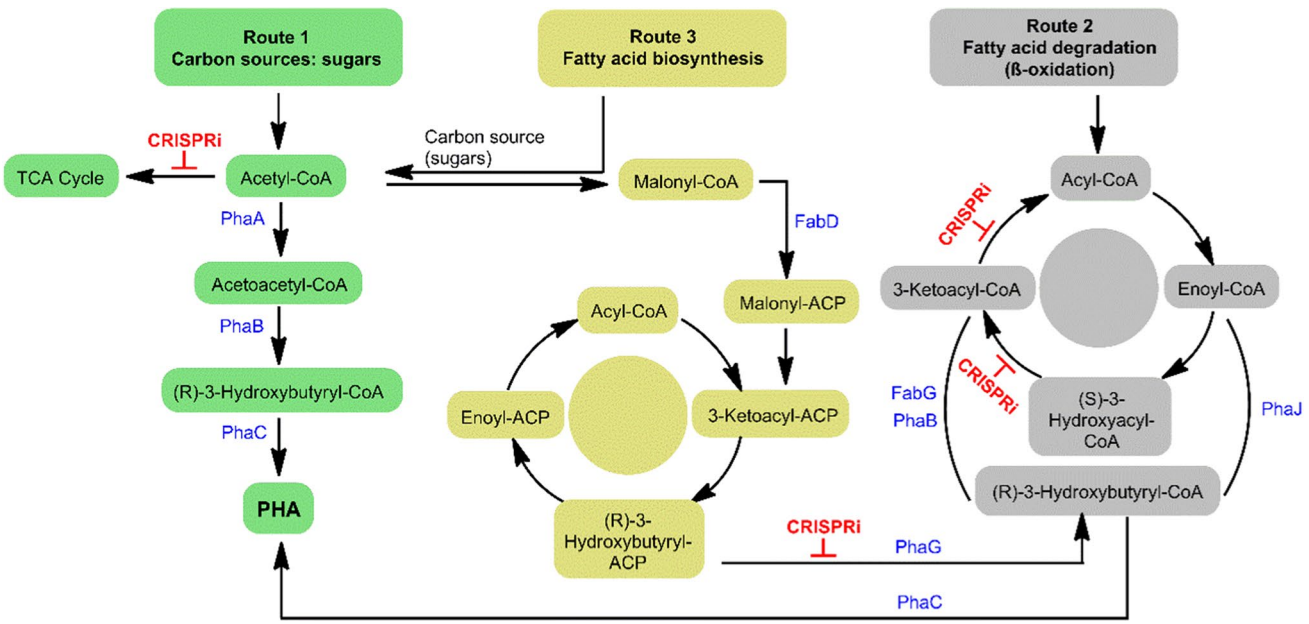

Fig. 2 Representation of metabolic pathways for microbial biosynthesis of PHAs (adapted from Kumar et al. 2020)

The CRISPR/Cas9 approach operates on the three main PHA biosynthesis pathways. In Fig. 2, it is possible to observe the target region of CRISPRi in the different metabolic routes of PHA production. In route 1, sugar as a carbon source, the CRISPRi acts in the regulation of genes of the products involved in the TCA cycle (e.g., acetyl CoA). In route 2, the CRISPRi acts in the conversion of the products hydroxyacyl CoA and acyl CoA. Finally, it also acts directly in the conversion of hydroxyacyl ACP into hydroxyacyl CoA in route 3. The role in gene modulation played by crispr/cas9 system is already known. It is possible to repress and overexpress genes of interest.

Manipulated organisms carrying genes related to PHA synthesis, named "chassis," are one of the critical factors for biosynthesis. Contamination-resistant and easily manipulated bacteria become useful for biotechnology that has additional advantages in PHA production. *Halomonas spp*. are examples of feasibility and challenges to develop a New Generation Industrial Biotechnology (NGIB) in PHA production more competitively. NGIB depends on these microorganisms for continuous large-scale bioproduct production to occur (Chen and Jiang 2018). In recent years, biological evolution is observed to improve biosynthesis efficiency and optimize the industrial production of PHA. Strategies include redirecting metabolism for PHA synthesis, increasing cell size, accelerating cell growth, and reprogramming biosynthesis by CRISPR/Cas9. If successful, the reprogrammed organisms should be able to grow under open, continuous conditions for economic PHA production (Chen and Jiang 2018).

As shown in Fig. 2, PHA biosynthesis competes with other metabolic cycles and intermediaries, so regulation of competing pathways is critical so that more substrates are diverted into the PHA biosynthesis pathway. For example, PHB synthesis is regulated by the flux of acetyl-CoA, which can enter the tricarboxylic acid (CAT) cycle or serve as a precursor for PHB biosynthesis. The fate of acetyl-CoA can be induced by a nutrient limitation or microbial growth conditions (Sudesh et al. 2000). Under nutrient-limited conditions, there is an increase in intracellular NADH which inhibits key regulatory enzymes of the TCA cycle (citrate synthase and isocitrate dehydrogenase), resulting in down-regulation of the TCA cycle. As a consequence, acetyl-CoA does not participate in the TCA cycle, accumulating inside cells. Accumulation of acetyl CoA occurs simultaneously with the reduction of free Co-A levels, activating the β-ketothiolase enzyme of the PHB synthetic pathway (Sudesh et al. 2000; Obruca, Sedlacek and Koller 2021).

Although the biosynthetic pathways of PHA are well investigated, there are still aspects that are not understood about the physiology of the microorganisms that produce this biopolymer. The optimization of cultivation conditions is another important factor in the metabolic regulation for PHA production, mainly for industrial-scale processes. Culture conditions include carbon, nitrogen, phosphate, dissolved oxygen, pH, carbon to nitrogen and phosphate ratios, trace elements, and supplement levels. Supplements are substances that are not essential for microbial growth but can trigger specific biosynthetic pathways and significantly increase PHA titer and productivity. Nutrient limitation and culture medium conditions can trigger PHA accumulation to higher intracellular levels (Li and Wilkins 2020).

Strategies for PHA production from agro-industrial residues

Currently, PHA production represents only 1.2% of total bioplastic production. The main cause of this low percentage is the cost associated with its production, about 2–3 times higher than the production of conventional plastics. The use of alternative carbon sources has been a strategy used to lower the price of the product, exerting a positive impact on production at the industrial level (Arumugam et al. 2019; Sehgal; Gupta 2020). The availability of renewable resources, mainly, agro-industrial by-products, is an excellent strategy to decrease the production costs of polyhydroxyalkanoates. In addition, the same by-product can be used by different bacteria to generate a PHA with different molecular compositions (Jian et al. 2016).

Polyhydroxyalkanoates are manufactured by several companies around the world: Metabolic (Woburn, MA, EUA), Procter & Gamble Co., Ltd. (Cincinnati, OH, EUA), Tianjin Green Bioscience Co., Ltd. (Tianjin, China) Bio on (Italy), Biocycle PHB Industry SA (São Paulo, Brazil) e Goodfellow Cambridge, Ltd. (UK), with variable annual production. According to the subtract used, it is possible to suggest which metabolic pathway the PHA was obtained, since each biosynthesis pathway depends on the source consumed by the microorganism (Fig. 2).

The substitution of expensive substrates such as glucose, mannitol, 1,4-butanediol, xylose, and fructose with cheaper carbon sources for the production of polyhydroxyalkanoates is extremely important to obtain economically viable products. Carbon sources from agro-industrial residues are organically rich materials and can be metabolized by a variety of microorganisms, such as: *Cupriavidus necator, Alcaligenes eutrophus*, *Wautersia eutropha* ou *Ralstonia eutropha*, *Alcaligenes latus*, *Aeromonas hydrophila*, *Pseudomonas putida,* and *Escherichia coli* (Albuquerque and Malafaia 2018). Table 1 lists the PHA-producing microorganisms and the wastes used to produce the bioplastic industrially.

Among the substrates used as a carbon source for PHA production, glycerol stands out. The rapid growth of the biodiesel industry has generated a significant amount of residual glycerol (RG), making it a promising carbon

Table 1 PHA producing companies and their global production (Jiang et al. 2016; Kumar et al. 2020; Koller and Mukherjee 2022; Tan et al. 2020)

Company	Country	Trade Names	Microorganism	Substrate	Types of PHA	Capacity (t/year)
Chemie Linz (technology transferred to Urs Hänggi)	Austria	n.r	*Azohydromonas lata*	Glucose from carbohydrates feedstocks	PHB	~50 (1980–1990)
PHB Industrial S.A. (PHB/ISA)	Brazil	Biocycles	*Cupriavidus necator*	Sucrose	PHB	~100 (entire PHA production capacity)
			Paraburkholderia sacchari	Hydrolyzed cane sugar	PHBHV	
			Bacillus spp.	Sucrose	PHB	
Bluepha Co. Ltd	China	Bluepha PHA	Rec. *C. necator*	Alternative carbon source (crops and kitchen waste)	PHBHHx	1000
COFCO	China	COFCO PHA	*Halomonas sp.* (*Halomonas bluephagenesis ssp.*)	Presumably glucose	PHB	1000
Medpha	China	Medpha PHA	*Halomonas spp.* (NGIB)	Glucose, corn steep liquor	P3HB4HB	100
PhaBuilder	China	mP34HB10	*Halomonas spp.* (NGIB[a])	Glucose, corn steep liquor	All types	1000–10,000
Shenzhen Ecomann Biotechnology Co. Ltd	China	AmBio	*Escherichia coli*	Sugar or glucose	P(3HB-*co*-4HB)	10,000 (planned: 75,000 capacity)
Tianan Biologic Materials Co	China	Enmat	*Ralstonia eutropha*	Dextrose deriving from corn and cassava grown in China	PHBV, PHBV + Ecoflex blend	10,000 and 50,000 by 2020
Tianjin GreenBio Materials Co. Ltd	China	SoGreen	Rec. *E. coli* (Enterobacterium)	Glucose and 1,4-butanediole (4HB precursor)	P(3HB-*co*-4HB)	10,000
Biomers	Germany	Biomer	*Alcaligenes latus*	Sucrose	PHB	~900 (1990s to present)
Bio-On	Italy	Minerv-PHA	*C. necator*	Renewable materials (Sugar beets, molasses and products from agriculture)	PHA	10,000 (2008, current situation unclear)
Kanegafuchi Corporation Co. Ltd	Japan	AONILEX	*R. eutropha*	Plant oils	PHBHHx	3500–5,000 (1990 to present)
ICI (technology transferred to Metabolix)	UK	Biopol	*C. necator*	Glucose	PHBHV	600–800 (stopped in 1996)
RWDC Industries Ltd	Singapore and USA	Solon	Rec. *C. necator*	WCO	PHBHHx	4000 (expected to be expanded)
Metabolix (IP sold to CJ, Korea)	USA	Metabolix	*E. coli*	Switchgrass	P3HB4HB	5,000 (1980 to present)

source for the production of polyhydroxyalkanoates by bacterial fermentation. Albuquerque et al. (2018) evaluated the production of the biopolymer from fermentation using the bacterium *C. necator*. During biomass production, the researchers verified a 35.75 and 45.08% consumption of pure glycerol (PG) and crude glycerol (CG), respectively, indicating higher PHA accumulation in PG.

Ntaikou et al. (2018) studied the accumulation efficiency of PHA produced from acidified residual glycerol (ARG) by pure microbial cultures (PMCs) and mixed cultures (MMCs). Maximum accumulation capacity occurred in MMCs with 40% PHA per dry cell mass. The lowest accumulation capacity was observed for residual non-acidified glycerol, which led to the formation of P(3HB), while

in the presence of ARG and its derivatives (propionate or hexanoate) PHA with different monomeric compositions was produced. Other studies using commercial glycerol, residual glycerol, and substrate mixtures are presented in Table 2.

Residual sources of lipids such as cooking oil and residues from vegetable oil production have attracted the attention of researchers since the 1990s because of their low cost and wide availability (Chee et al. 2019). The peanut oil (*Arachis hypogea*) was reported by Pérez-Arauz et al. (2019) as a carbon source in PHA production using the bacterium *C. necator*. At the end of the fermentation process, 26.8% peanut oil was consumed with 51% PHA accumulation. Table 3 shows studies performed with lipid substrates with different microorganisms and the PHA yield obtained for each substrate.

Whey is one of the main by-products of the dairy industry, obtained during cheese production. According to Amaro et al. (2019), there is an annual production of 120 million tons of whey worldwide, and only 50% of its volume is used for food production. The large availability of this by-product and the amount of carbohydrates present in its constitution make cheese whey a promising substrate for PHA production.

The study conducted by Das et al. (2018) evaluated ultrafiltered whole cheese whey for P(3HB) production by *B. megaterium* NCIM 5472 with 75% P(3HB) accumulation. Raho et al. (2020a, b) used cheese whey for PHA production using the bacterium *Haloferax mediterranei* obtaining 1.18 g/L of PHA. Other research using whey-based waste and PHA-producing microorganisms is available in Table 4.

Agroindustrial residues have gained notoriety and are considered relevant substrates for the production of PHAs on an industrial scale (Chee et al. 2019). Rao et al. (2019) used different agricultural residues as the sole source of carbon and nitrogen for the production of PHAs by *Bacillus subtilis* MTCC 144. The concentrations of these sources were statistically optimized using response surface methodology (RSM), associated with the genetic algorithm approach. Among the residues used, watermelon rinds and legume peels were the most suitable showing recovery of 78.60% PHA.

The sugar cane molasses, vinasse, starch, and lignocellulosic materials are favorable feedstocks for PHA production.

Table 2 Glycerol residues used in the production of PHA

Substrate	Microorganism	PHA Type	Yield	References
Crude glycerol	Recombinant *E. coli* ABC_{Ah}	P(3HB-co-3HH)	14%	Phithakrotchanakoon et al. 2015
Crude glycerol	*C. necator* DSM 545	P(3HB-c-4HB)	36.1%	Cavalheiro et al. 2012
Glycerin and 1,4 butanediol	*Cupriavidus* sp. USMAHM13	P(3HB-co-4HB)	48%	Ramachandran and Amirul 2013
Crude glycerol	*C. necator* DSM 545	P(3HB)	71%	Gahlawat and Soni 2017
Crude glycerol and activated sludge	*Alphaproteobacteria Betaproteobacteria*	HB-HV	80%	Fauzi et al. 2019
Crude glycerol	*Bacillus sp.* ISTVK1	PHV	85.2%	Morya et al. 2018
Crude glycerol	*C. necator* DSM7237	P(3HB)	86.2%	Kachrimanidou et al. 2014
Residual glycerol	*Cupriavidus necator*	P(3HB-co-3HV)	96%	Gahlawat et al. 2019
Mineral medial supplemented with glycerol	*Paracoccus sp. LL1*	P(3HB-co-3HV)	39,3%	Kumar et al. 2018

Table 3 Lipid substrates used in PHA production

Carbon source	Microorganism	PHA Type	Yield	References
Used cooking oil	*C. necator* DSM 428	PHB	37%	Martino et al. 2014
Waste water with ground oil	*H. mediterranei* DSM 1411	P(3HB-co-3HV)	43%	Alsafadi and Al-Mashaqbeh 2017
Soy oil	*Pseudomonas aeruginosa*	PHB	50,27%	Abid et al. 2016
Coconut oil	*Pseudomonas mendocina*	*mcl*-PHAs	58%	Basnett et al. 2018
Olive oil distillate	*Pseudomonas resinovorans*	*mcl*-PHA	62%	Cruz et al. 2016
Canola oil	*C. necator* ATCC 17,699	*mcl*-PHA	90%	López-Cuellar et al. 2011
Palm oil	*Cupriavidus* recombinant *Re2058/pCB113*	*PHB*	74%	Thinagaran and Sudesh 2017
Palm Olein	*Cupriavidus* recombinant *Re2058/pCB113*	P(3HB -co-3HHx)	39.8%	Hairudin, Ganesan and Sudesh 2020
Palm oil	*Cupriavidus necator*	P (3HB-co-3HHx)	18%	Tan et al. 2020
Linear olefins	*Pseudomonas putida*	mcl-PHA	65%	Dong et al. 2018

Table 4 Whey waste used for PHA production

Substrate	Microorganism	PHA Type	Yield	References
Cheese whey	*B. megaterium* CCM2307	PHB	51%	Obruca et al. 2011
Cheese whey	*H. mediterranei* ATCC 33,500	P(3HB-co-3HV)	53%	Pais et al. 2016
Lactose and whey	*Alcaligenes latus* DSM 1123	3HB	84%	Berwig et al. 2016
Cheese whey	Mixed microbial cultures	PHBV	45%	Oliveira et al. 2018
Cheese whey	*Haloferax mediterranei*	PHBV	62%	Raho et al. 2020a, b
Cheese whey and glucose	*B. megaterium* Ti3	P3HB	0.85 $g.L^{-1}$	Israni et al. 2020
Cheese whey	*Bacillus flexus* Azu-A2	PHB	20.96%	Khattab et al. 2021
Cheese whey	*Bacillus sp. CYR-1*	PHA	0.41 $g.L^{-1}$	Chang et al. 2021

The use of molasses as a by-product for PHA production is an excellent production strategy, since molasses contains significant amounts of minerals, essential for biomass growth, and the use of this waste decreases the costs associated with its disposal. Other research using the above-mentioned substrates is present in Table 5.

According to Nielsen et al. (2017) many agro-industrial substrates despite having all the advantages mentioned above, have very complex chemical compositions requiring pretreatment before being used as alternative carbon sources during the production process. Acid or enzymatic hydrolysis is commonly used pretreatments to convert the different renewable carbon sources into fermentable sugars. During the sample pretreatment step, there is the production of growth inhibitors, and consequently, there is a decrease in the production yield, making it necessary to add new procedures to eliminate these inhibitors.

When crude glycerol is used as a substrate for bioplastic production, the number of inorganic salts, methanol, and organic acids can cause a decrease in production yield. The reduction of bacterial growth, an essential step during PHA production, is related to methanol in the substrate that can be removed from the alcohol evaporation (Cavalheiro et al 2012).

Acid hydrolysis of lignocellulosic materials produces microbial growth inhibitors such as phenolic and aromatic compounds are released specifically from lignin, and furans are produced by the dehydration of pentoses and hexoses and organic acids produced from the acetyl group cleavage of hemicellulose or thermochemical degradation products. These compounds need to be removed from the hydrolysate to increase the yield of the PHA, and this can be done using membrane filtration techniques, evaporation of volatile compounds, ion exchange resins, and even the use of microorganisms that are able to degrade the inhibitors before fermentation (Obruca et al. 2015).

Other wastes such as cooking oil and cheese whey have the advantage of not requiring pretreatment and can be added directly to the growth medium to produce the biopolymer. This strategy is an excellent alternative for the reuse of oil, minimizing the environmental pollution caused when this material is discarded in the environment (Nielsen et al. 2017). Currently, industries use agro-industrial residues for PHA production according to Table 1.

Table 5 Agro-industrial residues used as carbon sources for PHA production

Carbon source	Microorganism	PHA Type	Yield	References
Apple pulp	*Pseudomonas citronellolis*	*mcl*-PHA	30%	Rebocho et al. 2019
Rice husk	*B. mycoides* DFC1	P(3HB-co-3HV)	34.5%	Narayanan et al. 2014
Sugarcane bagasse hydrolyzate	*Burkholderia sp*. F24	PHB	44%	Lopes et al. 2011
Cassava waste	*Halogeometricm borinquense* E3	P(3HB-co-3HV)	44.7%	Salgaonkar et al. 2019
Potato starch	*R. eutropha*	PHB	52.5%	Haas et al. 2014
Vinasse and sugar cane molasses	*C. necator*	PHB	56%	Dalsasso et al. 2019
Pineapple peel waste	*Ralstonia eutropha*	PHB and PHV	60%	Castro et al. 2016
Corn steep liquor	*Halomonas bluephagenesis*	P(3HB-co-4HB)	74%	Ye et al. 2018
Rice bran hydrolyzate	Recombinante *E. coli* XL1-Blue	PHB	90,1%	Oh et al. 2015
Rice milling	*Acinetobacter junii*	PHB	94,3%	Sabapathy et al. 2018

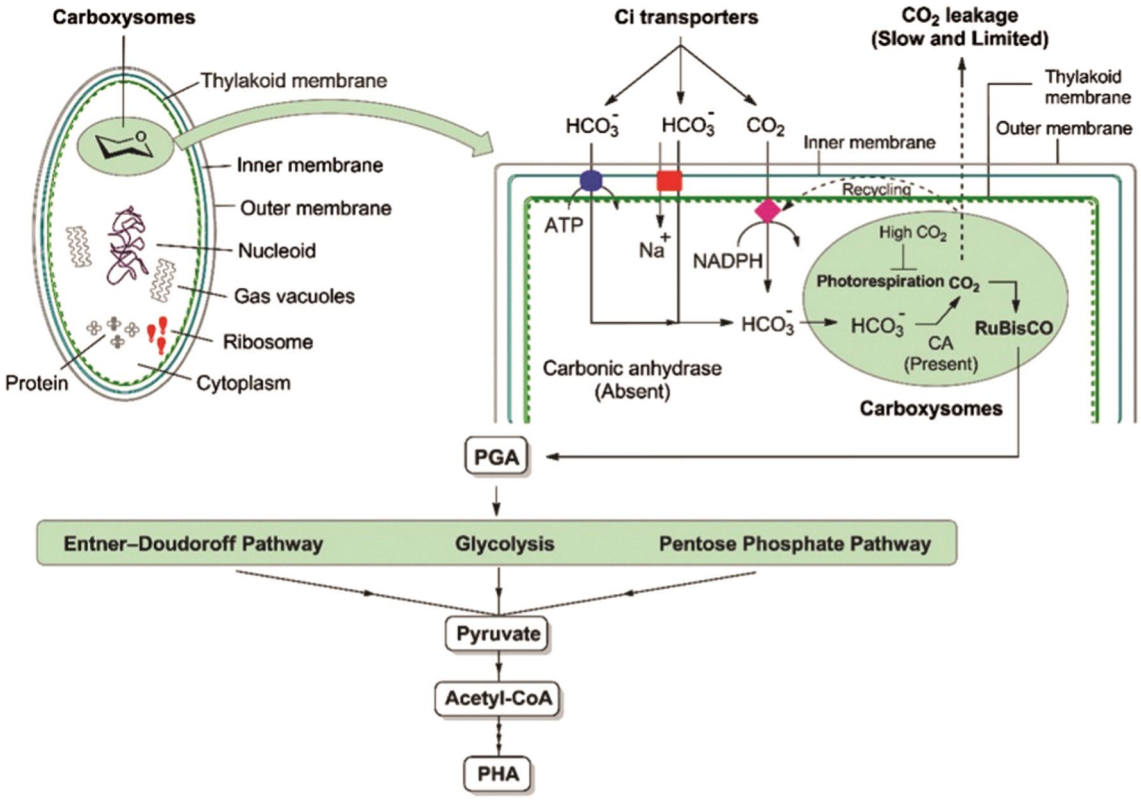

Fig. 3 PHA conversion from carbon accumulation and CO_2 fixation in cyanobacteria (adapted from Afreen et al. 2021)

The use of photosynthesizing microorganisms as producers of polyhydroxyalkanoates

Algae have long been investigated as a plausible reserve of several compounds, attributed to their fast-growing characteristics and short doubling time. Compounds extracted from algae are being studied in various pharmaceutical, cosmetic, cancer biology, nanoscience, food, and environmental industries (Zhang et al. 2020). Algae produce a range of basic materials that can be used to assemble bioplastics. Poly-3-hydroxybutyrate (PHB) is a polymer that is a type of PHA that is widely explored commercially and has excellent potential as biodegradable plastics and bioderivatives (Mendhulkar and Shetye 2017; Abdo and Ali 2019). There are two types of algae: microalgae and cyanobacteria, the latter also known as blue green algae. These photosynthetic microorganisms are capable of synthesizing and accumulating polyhydroxyalkanoates under different cultivation conditions, including: photoautotrophic, heterotrophic, and mixotrophic (Roja et al. 2019). Under autotrophic conditions, cyanobacteria fix their carbon source in the Calvin–Benson–Bassham (CBB) cycle with the help of ribulose-1,5-bisphosphate carboxylase/oxygenase (RuBisCO). RuBisCO has a higher efficiency for CO_2 fixation than for O_2 and is known to be responsible for the assimilation of a large amount of carbon present in the earth's biomass. Inorganic carbon (Ci) carriers present in the cell wall transfer atmospheric CO_2, thus helping to maintain the carbon concentration for RuBisCO. The output of the Calvin cycle, glyceraldehyde-3-phosphate after its conversion to 3-phosphoglycerate (PGA), can then enter any of the three pathways for sugar metabolism, i.e., the Entner-Doudoroff (ED) pathway, glycolysis, pentose phosphate and be finally converted to acetyl-CoA for use in the synthetic PHA pathway according to Fig. 3 (Singh and Mallick 2017). Different cultivation strategies are used for the production of PHAs in algae, such as the use of standard media, deficiency or addition of some nutrients, modification of parameters such as salinity and gas exchange, including the use of effluents such as sewage. Table 6 shows different types of algae grown under different growing conditions and their respective PHA/biomass (w/w) yields.

Several cultivation models, extraction methods, and obtaining PHAs from algae are studied daily to obtain a better yield of the biopolymer. The table shows that the PHA yield can vary greatly depending on the form of cultivation. However, metabolic studies of the production and composition of these bioproducts in algae have not yet been achieved and extensive research is needed (Arias et al. 2020).

Table 6 Growth conditions and PHA yield in different types of algae

Algae	Growing Conditions	Yield	References
Aulosira fertilissima	Limitation of gas exchange	49.0%	Samantary and Mallick (2015)
Botryococcus braunii	BG-11 medium	16.4%	Kavitha et al. (2016)
Microalgae consortium	Sewer	31.0%	Rahman et al. (2015)
Nostoc muscorum	Phosphorus deficiency	69.0%	Bhati and Mallick (2015)
Nostoc muscorun	Glucose/Acetate/Nitrogen Deficiency	60.0%	Ansari and Fatma (2016)
Spirulina sp. LEB18	Nitrogen deficiency	30.7%	Coelho et al. (2015)
Spirulina sp. LEB-18	Nitrogen deficiency	12.0%	Costa et al. (2018)
Synechococcus elongates	Nitrogen deficiency	17.15%	Mendhulkar and Shetye (2017)
Synechococcus elongates	Phosphorus deficiency	7.02%	Mendhulkar and Shetye (2017)
Synechococcus subsalsus	Nitrogen deficiency	16.0%	Costa et al. (2018)
Synechocystis salina	BG-11 medium	5.5–6.6%	Kovalcik et al. (2017)

Conclusion

The use of petrochemical plastics causes tons of waste to accumulate all over the planet, causing serious environmental impacts. The development of biodegradable plastics is necessary and must unite biodegradability, economic viability, and the production of materials with desirable physicochemical properties for their application in industry.

The production of polyhydroxyalkanoates is an excellent alternative for replacing conventional plastics. These biopolymers are produced by a series of microorganisms that can metabolize various types of substrates, contributing to the reduction of waste and costs associated with the production of bioplastics.

Acknowledgements The authors gratefully acknowledge the financial support of the Conselho Nacional de Desenvolvimento Científico e Tecnológico—CNPq (Processes: 302143/2021-1; 302267/2021-2; 302284 /2021-4; 302170/2021-9) and Centro de Tecnologias Estratégicas do Nordeste (CETENE).

Declarations

Conflict of interest The authors declare that they have no conflict of interests.

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