Applications of Polyhydroxyalkanoates (PHA): A Review on Sustainable Biopolymer

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ABSTRACT

Polyhydroxyalkanoates (PHA) are a group of biopolymers that can be both biodegradable and biocompatible; several microorganisms synthesize these polymers as biotic intracellular carbon and energy repositories. Such Polyhydroxyalkanoates augur well to replace conventional plastics thanks to their environmentally friendly properties that aid sustainable development and circular bioeconomy. In particular, their multifunctional usage led to significant attention in the biomedical, agriculture, environmental management, and packaging industries. PHAs are used in regenerative medicine, tissue engineering, drug delivery systems, and surgical applications because they are biocompatible with human tissues and organs. As sustainable substitutes in food packaging and biodegradable consumer products, they help reduce pollution by plastic waste. In agriculture, PHAs improve soil and crop productivity through controlled-release bioremediation fertilizers and biodegradable mulching films while alleviating plastic pollution. Their commercialization potential is expanded with integration into biofuel, 3D printing, textile, and cosmetic production. Most remarkably, their value as a substitute for antibiotics in livestock feed demonstrates their contribution to sustainable animal husbandry.

Keywords: Polyhydroxyalkanoates (PHA), biodegradable biopolymers, biomedical applications, packaging industry, bioremediation, antimicrobial alternatives.

I. INTRODUCTION

As previously mentioned, Polyhydroxyalkanoates (PHAs) are polyesters created from PHAs-rich bacterial species for use as intracellular carbon and energy repositories [1], [2]. PHA first came to attention during Lemoigne's 1926 study, which illustrated the first identification of poly(3-hydroxybutyrate) (PHB) where it was considered an intracellular polymer in *Bacillus megaterium* [3], [4]. Afterwards, several studies confirmed the growing demand for PHAs due to their biodegradable, thermoplastic, and biocompatible properties which can be utilized within biomedical, industrial, and environmental endeavours [5], [6].

The preliminary research tried using agricultural and industrial waste as renewable feedstocks to optimize PHA biosynthesis [7], [8]. In the last decade, the introduction of metabolic engineering designs was proven to enhance microbial PHA yields, thus increasing its market value [9]–[11]. The latter studies focus on PHA-containing materials as feasible substitutes for plastics made from petroleum [12]–[14]. The advances in bioprocessing of further synthetic constructs will be discussed in detail in 2024. Post-2010, life cycle assessment (LCA) studies have proved that PHA-based PHA plastics have a more economical carbon footprint compared to normal polymers [15]. Besides, merging PHA production with waste valorization activities has created economically favourable methods in some studies where agro-industrial wastes have been used [11], [12], [16]. The latest development in microbial engineering broadened the scope of PHA monomers which PHA can possess tunable attributes for certain particular uses [16]–[18]. While progress has been made, the commercialization of PHAs on a larger scale is still constrained due to high costs of production and issues with scalability [10], [15], [19]. There has been no lack of effort in trying to meet bottom-line objectives utilizing mixed microbial cultures (MMCs) and engineered microbial consortia to improve PHA production [20]. In addition, the advancements in the PHA copolymer synthesis are expected to serve greater applicability in the areas of biomedicine, environmental remediation, and 3D printing [18], [21], [22]. The industrial biotechnology trends point towards a shift to bioeconomic systems, with PHAs assuming an important role in displacing traditional plastics [23]. It is predicted that the global PHA market will grow substantially by 2030 aided by stronger policy incentives and technological progress [22]. Moreover, there has been a recent focus on enhanced bioprocessing methods involving synthetic biology and AI-augmented fermentation, which make PHA production more efficient and economically attractive [24], [25].

II. APPLICATIONS OF POLYHYDROXYALKANOATES (PHAS)

Polyhydroxyalkanoates (PHA) presents itself as a new type of biodegradable polymer with potential uses in biomedicine, packaging, agriculture, 3D printing, and even textiles. Lately, PHAs have been recognized as eco-friendly solutions to plastics due to their aforementioned biodegradability, as well as mechanical properties, and biocompatibility render them suitable substitutes for petroleum-based plastics [26]–[28] . This portion of the text offers a comprehensive description of the industrial uses of PHAs with a focus on new developments and problems within this context.

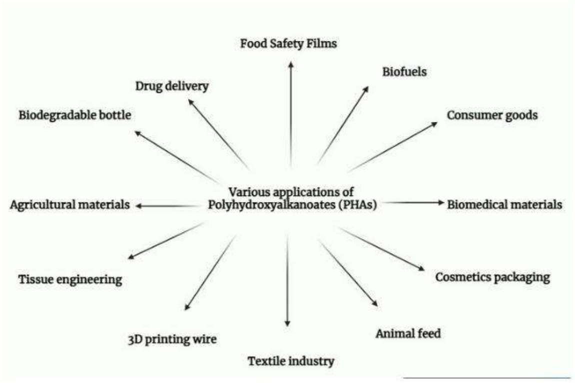

Fig. 1. Various Application of PHA

A. Biomedical Innovations Utilizing PHA

1) Biomedical Applications in Regenerative Medicine and Tissue Engineering : Due to biocompatibility, biodegradability, and non-toxic by-products upon degradation PHAs are considered promising biomaterials within medicine for tissue engineering, surgical implants, sutures, drug delivery, and even more advanced applications like using them in implants [29], [30]. Various PHA copolymers, like poly(3-hydroxybutyrate-co-3-hydroxyvalerate) (PHBV), have been investigated for scaffold fabrication for cell tissue engineering wherein they assist in cell proliferation and differentiation, thus, facilitating tissue regeneration [31].

2) Tissue Engineering and Regenerative Medicine : As a result of the biodegradability of PHA-based scaffolds, they are optimal for cell adhesion, proliferation, and differentiation, which in turn promotes renewal of damaged tissues. PHBV scaffolds have enhanced flexibility and mechanical strength, making them invaluable in the repair of bones and cartilage [32].

3) Bone and Cartilage Regeneration: Singh et al. (2021), Huang et al. (2024) explain that the greater incorporation of bioactive molecules in PHA scaffolds makes them more effective for bone and cartilage uses. In addition, PHA composites incorporating hydroxyapatite and other biomaterials are more effective due to enhanced osteointegration and thus better bone regeneration abilities [33]. These days, the scope of research in biomedicine constantly updates the knowledge of PHA-based materials and adjusts some of their features concerning the attainment of diverse aims in tissue engineering and regenerative medicine. Advances in nanotechnology, as well as in biofabrication, make PHAs promising biopolymers for innovative medical treatments.

4) Uses of Polyhydroxyalkanoates (PHA) in Drug Delivery Systems and Controlled Release Mechanisms: Owing to their versatility in encapsulating hydrophobic drugs and releasing them in controlled manners, Polyhydroxyalkanoates (PHAs) emerged as novel biomaterials for drug delivery use [34], [35]. PHAs have been effective in the creation of new bioactive compound delivery systems with PHA-based microparticles [36]. Surface modification of PHAs with functional groups to improve drug loading, targeting efficiency, and bioavailability has been the recent focus of research [22], [28]. The ability of PHA nano and microparticles to serve as carriers for the sustained and targeted delivery of therapeutic drugs opened a new research direction to improve therapeutic outcomes [37]. Other potential applications of PHA micelles and hydrogels include gene therapy, protein delivery, and vaccine delivery systems [38]. Most conventional sustained-release drug delivery systems use lactate and glycolate homopolymers and copolymers that are subjected to bulk hydrolysis-based degradation, thus making controlled drug release problematic [39]. However, since PHAs undergo surface erosion for biodegradation, they can provide better control of release [40].

Research has opened up the possibility of using poly(3-hydroxybutyrate-co-3-hydroxyvalerate) (PHBV) matrices for oral drug delivery, which eases processing and improves controlled release [41]. In addition, modifications to PHB microparticles have been found to affect the kinetics of drug release. Greater polymer molecular weight improves the release of sulfamethizole [42], whereas PHB carriers have been shown to outperform PLA microspheres in the release of anticancer drugs [43]. The incorporation of ethyl or butyl esters of fatty acids into PHB microspheres further increases the rate of drug release [44]. While PHB and PHBV are relatively the most researched PHA types, other PHA PHBV meta-ester PHA forms are also suggestive for better control of drug release. However, the integration of PHA metaalxethylates with sulphonamide group and PHB Methacrylates and 2-ethyl hexyl ester led to amphiphilic PHA that incorporate polymeric micelles and exhibit faster degradation PHB nanocarrier structures. A novel PHA granule binding protein drug delivery system (PhaP) has been created that uses PHA which acts as a hydrophobic polymer to attach to. Targeted delivery of drugs to macrophages and hepatocellular carcinoma cells has been conducted both in vitro and in vivo through the use of PhaP fused with certain ligands and PHA nanoparticles [45]. The transport of drugs was confirmed by the use of fluorescence microscopy using rhodamine B isothiocyanate (RBITC) while being tested on animal modes bearing tumours. The use of PHBV and other PHAs as drug delivery systems is therefore promising, as they are biocompatible and biodegradable. Their rapid degradation which allows controlled release of drugs is also important. Moreover, preliminary data suggests their potential for targeted delivery and drug encapsulation, making them suitable candidates for effective drug delivery systems.

5) Surgical Implants and Sutures : Polyhydroxyalkanoates, like Polyhydroxybutyrate (PHB), poly

-hydroxybutyrate – co – -hydroxy valerate (PHBV), Poly(4-hydroxybutyrate) (P4HB), Poly(3-hydroxybutyrate-co-3-hydroxyhexanoate) (PHBHHx), and Poly-3-hydroxy octanoate (PHO) are under consideration for biomedical use because of their compatibility and adjustable characteristics [46]–[48]. These materials offer an environmentally friendly substitute to conventional PHAs since they are biodegradable, making them suitable for surgical implants, including sutures, screws, bone plates, cardiovascular patches, nerve guides, and dressings [49], [50]. PHA-based sutures have both antimicrobial and self-degrading features which reduce the risk of infections and eliminate the need for removal [51]. Furthermore, PHA coating of cardiovascular stents and orthopaedic implants reduces inflammation enhancing recovery (34). Research has suggested that 3-hydroxybutyrate (3HB) helps PHAs to become suitable for tissue regeneration by promoting fibroblast proliferation while inhibiting cell apoptosis [51]. PHBHHx microparticles further enhance cell growth which is facilitated by modulation of intracellular calcium. This supports the potential use of PHBHHx in regenerative medicine [52]. PHAs are still one step ahead of biopolymers as candidates for next-generation surgical materials because of their controllable degradation rates [26], [53].

III. INDUSTRIAL APPLICATIONS OF POLYHYDROXYALKANOATES (PHA)

A. Packaging Industry

PHAs are gaining attraction for use in food packaging, consumer products, and sustainable plastics, thanks to their biodegradability and mechanical strength [54].

1) Food Packaging : Due to their biodegradability, polyhydroxyalkanoates (PHA) are increasingly being recognized as an environmentally friendly option in food packaging. Initially, a German firm, Wella, used PHA for shampoo bottle packaging [55]. More recently, Procter Gamble, Biomers, and Metabolix utilized PHA for food packaging films, shopping bags, and compostable packaging materials PHA-based films were developed [56], [57]. PHA-based films are almost perfect for food packaging because they are moisture-proof and gas-impermeable, making them useful for food wraps and storage containers [58].

2) Biodegradable Consumer Goods : Polyhydroxyalkanoates (PHAs) are gaining popularity for use as eco-friendly substitutes for oil-derived plastics in single-use cutlery, straws, shopping bags and containers [59]. Furthermore, PHA coating on paper cups and containers enhances water resistance while still allowing for composting, thus providing eco-friendly packaging alternatives [60]. In addition to food packaging, PHA have been blended into a variety of biodegradable consumer products. Extensively used in the manufacture of disposables such as razors, cups, diapers, feminine hygienic items, cosmetic containers, etc. In addition, PHA-containing materials are also important in industrial and medical fields as surgical garments, carpets, upholstery, and molded products such as lids and tubs [56], [57]. Researchers have aimed at crystallization and rupture tensile strength improvement to address the brittleness of PHA and aid its mechanical properties. Tanaka et al. (2007) produced high-strengthpolyhydroxybutyrate (PHB) fibres by stretching the fibres after controlled crystallization at glass transition temperature. In the same way, Vogel et al. (2007) enhanced PHB crystallization during the melt-spinning process using peroxide by reactive extrusion. This method not only enhanced fibre formation but also decreased the secondary crystallization thus resulting in strong fibers with good commercial prospects.

IV. AGRICULTURAL AND ENVIRONMENTAL APPLICATIONS

PHAs have a strong impact in the field of sustainable agriculture and pollution control such as in the use of controlled released fertilizers, biodegradable films, and bioremediation [61].

A. Controlled-Release Fertilizers

According to Ahn et al. (2022), PHA-based encapsulation systems have been observed to enhance fertilizer retention and diminish nutrient runoff and pollution due to their gradual release of nutrients. The incorporation of bio-based fertilizers is supported by Wang et al. (2023), who credits the enhanced soil microbial activity derived from PHAs as an advantage towards sustainable agriculture. Furthermore, PHA-based formulations have been noted to aid the survival of microbial inoculants under environmental stresses such as acidity, desiccation, and pesticides [62]. In laboratory field trials, the inoculants were noted to enhance the colonization of roots by the PHB-rich Azospirillum brasilense, thereby increasing plant growth and maize and wheat yields [63], [64]. In addition, PHA granules as carriers of insecticides PHA-degrading bacteria help to increase the application efficiency because of their controlled release when the polymer is broken down [65].

B. Biodegradable Agricultural Films

According to Bhatia et al. (2023), PHA-based agricultural films serve as compostable substitutes to traditional plastic mulches by controlling soil temperature, limiting the growth of weeds, and retaining moisture. Their decomposition in the soil also helps prevent the pollution caused by microplastics while enhancing soil health [66]. At the same time, their ability to integrate with microbial inoculants fosters soil fertility and plant growth. Unlike conventional plastic products, PHA-based films have the unique ability to fully biodegrade without too much leaving harmful byproducts, thus making them a suitable material for agriculture [61].

C. Bioremediation and Waste Treatment

Recently, PHA biofilters and membranes havegained popularity in municipal wastewater plants for their efficiency in removing organic pollutants [29]. Further, PHA acts as a carbon source in the microbial degradation process and increases the efficiency and longevity of the bacterial inoculants used for bioremediation [67]. There is some data that PHA-based carriers are more efficient in delivering the beneficial organisms to the polluted medium and therefore sustain the activity of degrading pollutants and restoration of soil fertility [1].

D. PHA as Biofuels

Recent studies indicate that Polyhydroxyalkanoates(PHAs) can be used as biofuels. As Zhang et al., (2009) reported, the combustion heats of poly-3-hydroxybutyrate methyl ester (3HBME) and medium-chain-length poly-3-hydroxyalkanoate methyl ester (3HAME) produced from the esterification of PHB and mcl-PHA had kJ/g as 20 and 30 respectively, which is 23 less than ethanol (27kJ/g) combustion heat. The blending of ten percent of 3HBME or 3HAME with ethanol produced better results.Fuel blends with diesel and gasoline have lower combustion heat compared with fossil fuels. I'm estimating the production cost of biofuels from PHA to be around $1200 per ton which makes them plausible for being renewable energy resources [68].

V. 3D PRINTING AND TEXTILE INDUSTRY

The growing usage of PHAs in the fields of additive manufacturing and sustainable textiles stems from their biodegradability as well as mechanical properties. PHAs (Polyhydroxyalkanoates) can be produced in the form of fibres, which makes them potential replacements for nylon in the textile industry. To achieve PHA's desired mechanical and economic properties blending it with polylactic acid (PLA) is necessary [55]. PLA is brittle and has a slow crystallization rate but polymerized with PHA and gains durability to ageing and less secondary crystallization [69]. Blends such as PLA/PHBV are used in knitted textiles and have been shown to maintain thermo-mechanical properties and have softness and strength [70]. Also, melt-spun PLAB/PHBV fibres have been proven to be strong, heat resistant and flexible. Likewise, dual-core spinning increases durability [71]. Vogel et al. (2007) document the use of peroxide in reactive extrusion processing to reduce the secondary crystallization of fibres, which improved their strength. Medical textiles and padding have already been PHA-impregnated by companies like PG, Biomers and Metabolix [72]. There has also been some work on the use of melt-spun, gel spun and electrospun PHA fibres for sustainable apparel. COFCO and PhaBuilder are some of the Chinese companies that use PHA for textiles [73]. As Kovalcik (2021) writes, PHA is becoming very popular for use in 3D printing, which is defined as an automated technology that fabricates three-dimensional objects from digital files using CAD software. Tissue engineering has received the most attention among the many applications of PHA in the aerospace, health, and pharmaceutical industries, primarily because of its biodegradability and biocompatibility [74]. One disadvantage is the low impact resistance and high stiffness and temperature of fusion (170–180°C) of PHB, which makes it unsuitable for 3D printing. Flexible copolymers like PHBV, P(3HB-co-3HHx) and P(3HB-co-4HB) are more pliable [75]. The most popular techniques for 3D printing PHA include selective laser sintering (SLS) and fused deposition modelling (FDM) [76].SLS has been utilized for scaffolds containing Ca-P/PHBV due to its capability to control the porous structure conducive for tissue engineering [77], [78]. More so, SLS Ca-P/P3HBV scaffolds are designed with drug delivery systems in mind [79]. Although PHA is not very thermally processable, it is stably fused in SLS printing [75].Fused deposition modelling (FDM) is defined as a melt-extrusion-based technique that involves building three-dimensional objects from thermoplastic filaments in successive horizontal layers [80]. The successful application of FDM often implies the use of copolymerization methods such as the incorporation of 3-hydroxyvalerate (PHBV), which elementary increases the thermal stability of the polymer [81]. In prior research, it has been proven that FDM can be applied to esterified PHBV filaments with additives like carbon nanotubes, palm fibre, or silicone sponge which enhance the mechanical performance of the printed part [82], [83].In addition, wood flour-reinforced PLA/PHA composite filament was shown to be extrudable with a temperature diffusion of 250 °C [84]. Further, blending 20% PHA with PLA was proven to greatly increase the ductility of PLA filaments by ensuring good distribution of PHA in the PLA matrix [85], [86]. A new method of 3D printing with PHA which is highly promising is stereolithography, but it needs a delicate optimization of photopolymerization by adjusting the polymer molecular weight and functional end groups [75].

VI. USE OF PHA IN THE COSMETIC INDUSTRY

Due to its characteristics such as biocompatibility, biodegradability, and plastic-like properties, Polyhydroxyalkanoates (PHAs) are becoming of interest within the cosmetic and skincare market. These uses include beauty masks, sanitary pads, and cast films [87]. PHA based oil blotting films have a highly porous and smooth surface which makes them easy to use as oil adsorbents [88]. In addition, other bio-based materials PHAs composites can be found in some commercial products like PolyBioSkin in the EU [87]. Effects of alpha-hydroxy acids on biochemical processes indicate that PHA compounds have a significant concern for water retention, being an antioxidant, and inhibiting matrix metallo proteinases, making them useful for skincare products [89]. PHA microplastics, unlike normal ones found in cosmetic and personal care products, do not degrade, thus preventing environmental pollution and seafood contamination for humans [87]. In addition, PHA compounds can form surface active agents exhibiting a degree of antibacterial activity which depends on the composition and surface structure. These effects are enhanced with the addition of essential oils and other antimicrobial bioactive compounds. For example, a MoS2 nanoparticle-embedded PHA-chitosan matrix exhibited anti-multi-drug resistant *Escherichia coli* K1 activity [90].

VII. PHA AS AN ANTIBACTERIAL GROWTH PROMOTER IN ANIMAL DIETS

The growing concern over antibiotic resistance has shifted the interest not only to PHAs as a growing medium of single-cell antibodies, but also to use them in animal nutrition and healthcare. Recent studies note the possibility of using PHA-bound single-cell proteins SCPs obtained from agricultural and industrial waste as a nutritious and antibacterial feed supplement in fish farming [91]. In potential parasitic species, medium-length chain PHAs produced by *Zobellella denitrificans* ZD1 and Pseudomonas oleovorans had shown good inhibition of pathogens and enhanced disease resistance.As PHAs have some antibacterial activity, they can also serve as immunostimulants and antibiotic substitutes in fish and shrimp farming [92]. Apart from aquaculture, PHAs have drawn attention because of their biodegradability and potential use in antibacterial treatments where research is being conducted into their modification with antimicrobial agents to improve bacterial resistance [93]. Even with their most positive results, there is still more work to be done in understanding the molecular mechanisms behind these and optimizing their use across various domains.

VIII. USING PHA IN MULCHING FILM

Mulching films made from PHA are more environmentally friendly than polyethylene mulch which is not biodegradable and causes environmental pollution [94]. These biodegradable films assist in retaining soil moisture while having the ability to improve soil structure and suppress weed growth, thus enhancing soil health [95]. Their degradation rate varies with climatic and crop conditions, which makes these films appropriate for sustainable farming (107,Park et al., 2024). Moreover, scl-PHA is applicable in controlled-release fertilizers, thereby aiding carbon-negative farming. Some companies such as Danimer Scientific and Metabolix have produced agricultural PHA-based mulch (Randon Attard, 2007).

IX. CONCLUSION

The use of PHAs in agriculture and biopolymer science shows promise as they are applicable in medicine, industry, and even farming.The adoption of a circular bioeconomy and the mitigation of the repercussions of climate change is particularly relevant given their ability to substitute petroleum-sourced plastics. Nonetheless, affordable fabrication, bulk commercial processing, and customization of desired material characteristics are some of the issues that need to be resolved for extensive commercialization. More efficient fermentation processes, genetic engineering of the microorganism's metabolism towards higher output, and the adoption of PHA products by global industries are likely to be targeted in subsequent investigations. With these advances, PHAs will be one of the primary players in fostering modern plastic waste management approaches while stimulating green technological development in numerous fields.

REFERENCES

[1] A. Steinbüchel and B. Füchtenbusch, "Bacterial and other biological systems for polyester production," Trends in biotechnology, vol. 16, no. 10, pp. 419–427, 1998.
[2] T. Keshavarz and I. Roy, "Polyhydroxyalkanoates: bioplastics with a green agenda," Current opinion in microbiology, vol. 13, no. 3, pp. 321–326, 2010.
[3] M. Lemoigne, "Produit de déshydratation et de polymérisation de l'acide β-oxybutyrique," Bull. Soc. Chim. Biol., vol. 8, pp. 770–782, 1926.
[4] A. J. Anderson and E. Dawes, "Occurrence, metabolism, metabolic role, and industrial uses of bacterial polyhydroxyalkanoates," Microbiological reviews, vol. 54, no. 4, pp. 450–472, 1990.
[5] K. Sudesh, H. Abe, and Y. Doi, "Synthesis, structure and properties of polyhydroxyalkanoates: biological polyesters," Progress in polymer science, vol. 25, no. 10, pp. 1503–1555, 2000.
[6] J. Możejko-Ciesielska and R. Kiewisz, "Bacterial polyhydroxyalkanoates: Still fabulous?," Microbiological research, vol. 192, pp. 271–282, 2016.
[7] S. Khanna and A. K. Srivastava, "Recent advances in microbial polyhydroxyalkanoates," Process biochemistry, vol. 40, no. 2, pp. 607–619, 2005.
[8] A. Anjum, M. Zuber, K. M. Zia, A. Noreen, M. N. Anjum, and S. Tabasum, "Microbial production of polyhydroxyalkanoates (phas) and its copolymers: A review of recent advancements," International journal of biological macromolecules, vol. 89, pp. 161–174, 2016.
[9] G.-Q. Chen and X.-R. Jiang, "Engineering bacteria for enhanced polyhydroxyalkanoates (pha) biosynthesis," Synthetic and systems biotechnology, vol. 2, no. 3, pp. 192–197, 2017.
[10] C. Kourmentza, J. Plácido, N. Venetsaneas, A. Burniol-Figols, C. Varrone, H. N. Gavala, and M. A. Reis, "Recent advances and challenges towards sustainable polyhydroxyalkanoate (pha) production," Bioengineering, vol. 4, no. 2, p. 55, 2017.
[11] K. W. Meereboer, M. Misra, and A. K. Mohanty, "Review of recent advances in the biodegradability of polyhydroxyalkanoate (pha) bioplastics and their composites," Green Chemistry, vol. 22, no. 17, pp. 5519–5558, 2020.
[12] N. Wierckx, T. Narancic, C. Eberlein, R. Wei, O. Drzyzga, A. Magnin, H. Ballerstedt, S. T. Kenny, E. Pollet, L. Averous, et al., "Plastic biodegradation: Challenges and opportunities," Consequences of microbial interactions with hydrocarbons, oils, and lipids: biodegradation and bioremediation, pp. 1–29, 2018.
[13] K. Khosravi Darani, F. Yazdian, H. Rashedi, N. Madadian Bozorg, M. Moradi, S. Rezazadeh Mofradnia, and M. Koller, "Simulation of bioreactors for phb production from natural gas," Iranian Journal of Chemistry and Chemical Engineering, vol. 39, no. 1, pp. 313–336, 2020.
[14] G. Jiang, D. J. Hill, M. Kowalczuk, B. Johnston, G. Adamus, V. Irorere, and I. Radecka, "Carbon sources for polyhydroxyalkanoates and an integrated biorefinery," International Journal of Molecular Sciences, vol. 17, no. 7, p. 1157, 2016.
[15] M. Albuquerque, V. Martino, E. Pollet, L. Avérous, and M. Reis, "Mixed culture polyhydroxyalkanoate (pha) production from volatile fatty acid (vfa)-rich streams: effect of substrate composition and feeding regime on pha productivity, composition and properties," Journal of biotechnology, vol. 151, no. 1, pp. 66–76, 2011.
[16] Z. A. Raza, S. Abid, and I. M. Banat, "Polyhydroxyalkanoates: Characteristics, production, recent developments and applications," International Biodeterioration & Biodegradation, vol. 126, pp. 45–56, 2018.
[17] L. S. Dilkes-Hoffman, P. A. Lant, B. Laycock, and S. Pratt, "The rate of biodegradation of pha bioplastics in the marine environment: A meta-study," Marine Pollution Bulletin, vol. 142, pp. 15–24, 2019.
[18] S. Singh, B. Sithole, P. Lekha, K. Permaul, and R. Govinden, "Optimization of cultivation medium and cyclic fed-batch fermentation strategy for enhanced polyhydroxyalkanoate production by bacillus thuringiensis using a glucose-rich hydrolyzate," Bioresources and Bioprocessing, vol. 8, pp. 1–17, 2021.
[19] K. Dietrich, M.-J. Dumont, L. F. Del Rio, and V. Orsat, "Producing phas in the bioeconomy—towards a sustainable bioplastic," Sustainable production and consumption, vol. 9, pp. 58–70, 2017.
[20] S. P. Valappil, D. Peiris, G. Langley, J. Herniman, A. R. Boccaccini, C. Bucke, and I. Roy, "Polyhydroxyalkanoate (pha) biosynthesis from structurally unrelated carbon sources by a newly characterized bacillus spp.," Journal of Biotechnology, vol. 127, no. 3, pp. 475–487, 2007.
[21] T. Huang, Y. Zeng, C. Li, Z. Zhou, J. Xu, L. Wang, D.-G. Yu, and K. Wang, "Application and development of electrospun nanofiber scaffolds for bone tissue engineering," ACS Biomaterials Science & Engineering, vol. 10, no. 7, pp. 4114–4144, 2024.
[22] J. He, M. Tang, F. Zhong, J. Deng, W. Li, L. Zhang, Q. Lin, X. Xia, J. Li, and T. Guo, "Current trends and possibilities of typical microbial protein production approaches: a review," Critical Reviews in Biotechnology, vol. 44, no. 8, pp. 1515–1532, 2024.
[23] V. Kumar, A. R. Ashraf, and W. Nadeem, "Ai-powered marketing: What, where, and how?," International Journal of Information Management, vol. 77, p. 102783, 2024.
[24] R. W. Clarke, G. Rosetto, T. Uekert, J. B. Curley, H. Moon, B. C. Knott, J. E. McGeehan, and K. M. Knauer, "Polyhydroxyalkanoates in emerging recycling technologies for a circular materials economy," Materials Advances, vol. 5, no. 17, pp. 6690–6701, 2024.
[25] G.-Q. Chen and Q. Wu, "The application of polyhydroxyalkanoates as tissue engineering materials," Biomaterials, vol. 26, no. 33, pp. 6565–6578, 2005.
[26] M. Koller, "Advances in polyhydroxyalkanoate (pha) production," 2017.

[27] A. Singh and V. Srivastava, “Production of polyhydroxyalkanoates (pha) by pseudomonas from waste products,” International journal of health sciences, vol. 6, no. S3, pp. 11450–11459, 2022.

[28] E. Elmowafy, A. Abdal-Hay, A. Skouras, M. Tiboni, L. Casettari, and V. Guarino, “Polyhydroxyalkanoate (pha): Applications in drug delivery and tissue engineering,” Expert review of medical devices, vol. 16, no. 6, pp. 467–482, 2019.

[29] V. C. Kalia, S. K. Patel, and J.-K. Lee, “Exploiting polyhydroxyalkanoates for biomedical applications,” Polymers, vol. 15, no. 8, p. 1937, 2023.

[30] X.-H. Zhao, Y.-N. Niu, C.-H. Mi, H.-L. Gong, X.-Y. Yang, J.-S.-Y. Cheng, Z.-Q. Zhou, J.-X. Liu, X.-L. Peng, and D.-X. Wei, “Electrospinning nanofibers of microbial polyhydroxyalkanoates for applications in medical tissue engineering,” Journal of Polymer Science, vol. 59, no. 18, pp. 1994–2013, 2021.

[31] E. Shishatskaya and T. Volova, “A comparative investigation of biodegradable polyhydroxyalkanoate films as matrices for in vitro cell cultures,” Journal of Materials Science: Materials in Medicine, vol. 15, no. 8, pp. 915–923, 2004.

[32] I. Ielo, G. Calabrese, G. De Luca, and S. Conoci, “Recent advances in hydroxyapatite-based biocomposites for bone tissue regeneration in orthopedics,” International journal of molecular sciences, vol. 23, no. 17, p. 9721, 2022.

[33] S. Philip, T. Keshavarz, and I. Roy, “Polyhydroxyalkanoates: biodegradable polymers with a range of applications,” Journal of chemical technology & biotechnology: International research in process, Environmental & clean technology, vol. 82, no. 3, pp. 233–247, 2007.

[34] M. S. del Oso, R. Nair, M. Mauricio-Iglesias, and A. Hospido, “Comparative life cycle analysis of pha-based consumer items for daily use,” Resources, Conservation and Recycling, vol. 199, p. 107242, 2023.

[35] A. K. Singh, J. K. Srivastava, A. K. Chandel, L. Sharma, N. Mallick, and S. P. Singh, “Biomedical applications of microbially engineered polyhydroxyalkanoates: An insight into recent advances, bottlenecks, and solutions,” Applied microbiology and biotechnology, vol. 103, pp. 2007–2032, 2019.

[36] J. Li, D. Li, Y. Su, X. Yan, F. Wang, L. Yu, and X. Ma, “Efficient and economical production of polyhydroxyalkanoate from sustainable rubber wood hydrolysate and xylose as co-substrate by mixed microbial cultures,” Bioresource Technology, vol. 355, p. 127238, 2022.

[37] Z.-W. Ren, Z.-Y. Wang, Y.-W. Ding, J.-W. Dao, H.-R. Li, X. Ma, X.-Y. Yang, Z.-Q. Zhou, J.-X. Liu, C.-H. Mi, et al., “Polyhydroxyalkanoates: the natural biopolyester for future medical innovations,” Biomaterials Science, vol. 11, no. 18, pp. 6013–6034, 2023.

[38] C. W. Pouton and S. Akhtar, “Biosynthetic polyhydroxyalkanoates and their potential in drug delivery,” Advanced Drug Delivery Reviews, vol. 18, no. 2, pp. 133–162, 1996.

[39] P. L. Gould, S. J. Holland, and B. J. Tighe, “Polymers for biodegradable medical devices. iv. hydroxybutyrate-valerate copolymers as non-disintegrating matrices for controlled-release oral dosage forms,” International journal of pharmaceutics, vol. 38, no. 1-3, pp. 231–237, 1987.

[40] F. Koosha, R. Muller, and S. Davis, “Polyhydroxybutyrate as a drug carrier.,” Critical reviews in therapeutic drug carrier systems, vol. 6, no. 2, pp. 117–130, 1989.

[41] M. R. Brophy and P. Deasy, “In vitro and in vivo studies on biodegradable polyester microparticles containing sulphamethizole,” International journal of pharmaceutics, vol. 29, no. 2-3, pp. 223–231, 1986.

[42] M. Bissery, F. Valeriote, and C. Thies, “Therapeutic efficacy of ccnu-loaded microspheres prepared from poly (d, l) lactide (pla) or poly-b-hydroxybutyrate (phb) against lewis lung (ll) carcinoma,” in Proceedings of the American Association for Cancer Research, vol. 26, pp. 355–355, AMER ASSOC CANCER RESEARCH PUBLIC LEDGER BLDG, SUITE 816, 150 S . . . , 1985.

[43] M. KUBOTA, M. NAKANO, and K. JUNI, “Mechanism of enhancement of the release rate of aclarubicin from poly-β-hydroxybutyric acid microspheres by fatty acid esters,” Chemical and pharmaceutical bulletin, vol. 36, no. 1, pp. 333–337, 1988.

[44] Y. Wang, Y.-Z. Bian, Q. Wu, and G.-Q. Chen, “Evaluation of three-dimensional scaffolds prepared from poly (3-hydroxybutyrate-co-3-hydroxyhexanoate) for growth of allogeneic chondrocytes for cartilage repair in rabbits,” Biomaterials, vol. 29, no. 19, pp. 2858–2868, 2008.

[45] O. Hrabak, “Industrial production of poly-β-hydroxybutyrate,” FEMS Microbiology Reviews, vol. 9, no. 2-4, pp. 251–255, 1992.

[46] D. Byrom, “Production of poly-β-hydroxybutyrate: poly-β-hydroxyvalerate copolymers,” FEMS Microbiology Reviews, vol. 9, no. 2-4, pp. 247–250, 1992.

[47] G. Chen, G. Zhang, S. Park, and S. Lee, “Industrial scale production of poly (3-hydroxybutyrate-co-3-hydroxyhexanoate),” Applied microbiology and biotechnology, vol. 57, pp. 50–55, 2001.

[48] Z.-W. Dai, X.-H. Zou, and G.-Q. Chen, “Poly (3-hydroxybutyrate-co-3-hydroxyhexanoate) as an injectable implant system for prevention of post-surgical tissue adhesion,” Biomaterials, vol. 30, no. 17, pp. 3075–3083, 2009.

[49] Z. Wang, H. Wu, J. Chen, J. Zhang, Y. Yao, and G.-Q. Chen, “A novel self-cleaving phasin tag for purification of recombinant proteins based on hydrophobic polyhydroxyalkanoate nanoparticles,” Lab on a Chip, vol. 8, no. 11, pp. 1957–1962, 2008.

[50] I. N. Najar, P. Sharma, R. Das, K. Mondal, A. K. Singh, S. Tamang, P. Hazra, N. Thakur, R. Bhanwaria, S. Gandhi, et al., “In search of poly-3-hydroxybutyrate (phb): A comprehensive review unveiling applications and progress in fostering a sustainable bio-circular economy,” Food and Bioproducts Processing, 2024.

[51] S. Cheng, G.-Q. Chen, M. Leski, B. Zou, Y. Wang, and Q. Wu, “The effect of d, l-β-hydroxybutyric acid on cell death and proliferation in l929 cells,” Biomaterials, vol. 27, no. 20, pp. 3758–3765, 2006.

[52] H. Abe, Y. Doi, H. Aoki, T. Akehata, Y. Hori, and A. Yamaguchi, “Physical properties and enzymic degradability of copolymers of (r)-3-hydroxybutyric and 6-hydroxyhexanoic acids,” Macromolecules, vol. 28, no. 23, pp. 7630–7637, 1995.

[53] B. Tajeddin and M. Arabkhedri, “Polymers and food packaging,” in Polymer science and innovative applications, pp. 525–543, Elsevier, 2020.

[54] K. Stublic´, J. Ranilovic´, V. Ocelic´ Bulatovic´, and D. Kucˇic´ Grgic´, “Advancing sustainability: Utilizing bacterial polyhydroxyalkanoate for food packaging,” Processes, vol. 12, no. 9, 2024.

[55] R. M. Weiner, “Biopolymers from marine prokaryotes,” Trends in biotechnology, vol. 15, no. 10, pp. 390–394, 1997.

[56] A.-M. Clarinval and J. Halleux, “Classification of biodegradable polymers,” in Biodegradable polymers for industrial applications, pp. 3–31, Elsevier, 2005.

[57] G. Mikova and I. Chodak, “Properties and modification of poly (3-hydroxybutanoate),” Chemicke Listy, vol. 100, no. 12, p. 1075, 2006.

[58] M. Chaco´n, P. Wongsirichot, J. Winterburn, and N. Dixon, “Genetic and process engineering for polyhydroxyalkanoate production from pre- and post-consumer food waste,” Current Opinion in Biotechnology, vol. 85, p. 103024, 2024.

[59] S. S. Ali, E. A. Abdelkarim, T. Elsamahy, R. Al-Tohamy, F. Li, M. Kornaros, A. Zuorro, D. Zhu, and J. Sun, “Bioplastic production in terms of life cycle assessment: A state-of-the-art review,” Environmental science and ecotechnology, vol. 15, p. 100254, 2023.

[60] J. Cheng, R. Gao, Y. Zhu, and Q. Lin, “Applications of biodegradable materials in food packaging: A review,” Alexandria Engineering Journal, vol. 91, pp. 70–83, 2024.

[61] D.-Y. Kim, H.-W. Kim, M.-G. Chung, and Y.-H. Rhee, “Biosynthesis, modification, and biodegradation of bacterial medium-chain-length polyhydroxyalkanoates,” Journal of microbiology, vol. 45, no. 2, pp. 87–97, 2007.

[62] F. B. Rebah, D. Pre´vost, A. Yezza, and R. Tyagi, “Agro-industrial waste materials and wastewater sludge for rhizobial inoculant production: a review,” Bioresource technology, vol. 98, no. 18, pp. 3535–3546, 2007.

[63] E. Fallik and Y. Okon, “Inoculants of azospirillum brasilense: biomass production, survival and growth promotion of setaria italica and zea mays,” Soil Biology and Biochemistry, vol. 28, no. 1, pp. 123–126, 1996.

[64] S. Dobbelaere, A. Croonenborghs, A. Thys, D. Ptacek, J. Vanderleyden, P. Dutto, C. Labandera-Gonzalez, J. Caballero-Mellado, J. F. Aguirre, Y. Kapulnik, et al., “Responses of agronomically important crops to inoculation with azospirillum,” Functional Plant Biology, vol. 28, no. 9, pp. 871–879, 2001.

[65] P. Holmes, “Applications of phb-a microbially produced biodegradable thermoplastic,” Physics in technology, vol. 16, no. 1, p. 32, 1985.

[66] M. Albareda, D. N. Rodr´ıguez-Navarro, M. Camacho, and F. J. Temprano, “Alternatives to peat as a carrier for rhizobia inoculants: solid and liquid formulations,” Soil Biology and Biochemistry, vol. 40, no. 11, pp. 2771–2779, 2008.

[67] D. Kadouri, E. Jurkevitch, and Y. Okon, “Involvement of the reserve material poly-β-hydroxybutyrate in azospirillum brasilense stress endurance and root colonization,” Applied and Environmental Microbiology, vol. 69, no. 6, pp. 3244–3250, 2003.

[68] X. Zhang, R. Luo, Z. Wang, Y. Deng, and G.-Q. Chen, “Application of (r)-3-hydroxyalkanoate methyl esters derived from microbial polyhydroxyalkanoates as novel biofuels,” Biomacromolecules, vol. 10, no. 4, pp. 707–711, 2009.

[69] R. Jan-Georg, R. Langer, and T. Giovanni, “Bioplastics for a circular economy,” Nature Reviews. Materials, vol. 7, no. 2, pp. 117–137, 2022.

[70] M. Yang, J. Hu, N. Xiong, B. Xu, Y. Weng, and Y. Liu, “Preparation and properties of pla/phbv/pbat blends 3d printing filament,” Materials Research Express, vol. 6, no. 6, p. 065401, 2019.

[71] R. Hufenus, Y. Yan, M. Dauner, and T. Kikutani, “Melt-spun fibers for textile applications,” Materials, vol. 13, no. 19, p. 4298, 2020.

[72] R. Jerome, “New developments in the synthesis of aliphatic polyesters by ring-opening polymerisation r je´ro^me and p lecomte, university of lie`ge, belgium,” Biodegradable polymers for industrial applications, p. 77, 2005.

[73] A. Mukherjee and M. Koller, “Polyhydroxyalkanoate (pha) biopolyesters-emerging and major products of industrial biotechnology,” EuroBiotech J, vol. 6, no. 2, pp. 49–60, 2022.

[74] K. Zhang, Y. Fan, N. Dunne, and X. Li, “Effect of microporosity on scaffolds for bone tissue engineering,” Regenerative biomaterials, vol. 5, no. 2, pp. 115–124, 2018.

[75] A. Kovalcik, “Recent advances in 3d printing of polyhydroxyalkanoates: a review,” EuroBiotech J, vol. 5, no. 1, pp. 48–55, 2021.

[76] M. Mehrpouya, H. Vahabi, M. Barletta, P. Laheurte, and V. Langlois, “Additive manufacturing of polyhydroxyalkanoates (phas) biopolymers: Materials, printing techniques, and applications,” Materials Science and Engineering: C, vol. 127, p. 112216, 2021.

[77] K. Leong, C. Cheah, and C. Chua, “Solid freeform fabrication of three-dimensional scaffolds for engineering replacement tissues and organs,” Biomaterials, vol. 24, no. 13, pp. 2363–2378, 2003.

[78] B. Duan, M. Wang, W. Y. Zhou, W. L. Cheung, Z. Y. Li, and W. W. Lu, “Three-dimensional nanocomposite scaffolds fabricated via selective laser sintering for bone tissue engineering,” Acta biomaterialia, vol. 6, no. 12, pp. 4495–4505, 2010.

[79] B. Duan and M. Wang, “Customized ca–p/phbv nanocomposite scaffolds for bone tissue engineering: design, fabrication, surface modification and sustained release of growth factor,” Journal of the Royal Society Interface, vol. 7, no. suppl_5, pp. S615–S629, 2010.

[80] F. M. Mwema, E. T. Akinlabi, F. M. Mwema, and E. T. Akinlabi, “Basics of fused deposition modelling (fdm),” Fused deposition modeling: strategies for quality enhancement, pp. 1–15, 2020.

[81] A. Kovalcik, L. Sangroniz, M. Kalina, K. Skopalova, P. Humpol´ıcˇek, M. Omastova, N. Mundigler, and A. J. Mu¨ller, “Properties of scaffolds prepared by fused deposition modeling of poly (hydroxyalkanoates),” International Journal of Biological Macromolecules, vol. 161, pp. 364–376, 2020.

[82] C. Wu and H. Liao, “Interface design of environmentally friendly carbon nanotube-filled polyester composites: Fabrication, characterisation, functionality and application.,” Express Polymer Letters, vol. 11, no. 3, 2017.

[83] C.-S. Wu, “Characterization, functionality and application of siliceous sponge spicules additive-based manufacturing biopolymer composites,” Additive Manufacturing, vol. 22, pp. 13–20, 2018.

[84] S. Guessasma, S. Belhabib, and H. Nouri, “Microstructure and mechanical performance of 3d printed wood-pla/pha using fused deposition modelling: Effect of printing temperature,” Polymers, vol. 11, no. 11, p. 1778, 2019.

[85] P. Mencˇ´ık, R. Pˇrikryl, I. Stehnova´, V. Melcˇova´, S. Konta´rova´, S. Figalla, P. Alexy, and J. Bocˇkaj, “Effect of selected commercial plasticizers on mechanical, thermal, and morphological properties of poly (3-hydroxybutyrate)/poly (lactic acid)/plasticizer biodegradable blends for three-dimensional (3d) print,” Materials, vol. 11, no. 10, p. 1893, 2018.

[86] S. Konta´rova´, R. Pˇrikryl, V. Melcˇova´, P. Mencˇ´ık, M. Hora´lek, S. Figalla, R. Plavec, J. Feranc, J. Sad´ılek, and A. Posp´ısˇilova´, “Printability, mechanical and thermal properties of poly (3-hydroxybutyrate)-poly (lactic acid)-plasticizer blends for three-dimensional (3d) printing,” Materials, vol. 13, no. 21, p. 4736, 2020.

[87] M.-B. Coltelli and S. Danti, “Biobased materials for skin-contact products promoted by polybioskin project,” 2020.

[88] K. Sudesh, C.-Y. Loo, L.-K. Goh, T. Iwata, and M. Maeda, “The oil-absorbing property of polyhydroxyalkanoate films and its practical application: a refreshing new outlook for an old degrading material,” Macromolecular Bioscience, vol. 7, no. 11, pp. 1199–1205, 2007.

[89] B. Algiert-Zielin´ska, P. Mucha, and H. Rotsztejn, “Lactic and lactobionic acids as typically moisturizing compounds,” International journal of dermatology, vol. 58, no. 3, pp. 374–379, 2019.

[90] A. Sethulekshmi, J. S. Jayan, S. Appukuttan, and K. Joseph, “Mos2: Advanced nanofiller for reinforcing polymer matrix,” Physica E: Low-dimensional Systems and Nanostructures, vol. 132, p. 114716, 2021.

[91] F. Asiri and K.-H. Chu, “Valorization of agro-industrial wastes into polyhydroxyalkanoates-rich single-cell proteins to enable a circular waste-to-feed economy,” Chemosphere, vol. 309, p. 136660, 2022.

[92] A. S. Santhosh and M. Umesh, “A strategic review on use of polyhydroxyalkanoates as an immunostimulant in aquaculture,” Applied Food Biotechnology, vol. 8, no. 1, pp. 1–18, 2021.

[93] S. Ladhari, N.-N. Vu, C. Boisvert, A. Saidi, and P. Nguyen-Tri, “Recent development of polyhydroxyalkanoates (pha)-based materials for antibacterial applications: A review,” ACS Applied Bio Materials, vol. 6, no. 4, pp. 1398–1430, 2023.

[94] S. Bandopadhyay, L. Martin-Closas, A. M. Pelacho, and J. M. DeBruyn, “Biodegradable plastic mulch films: impacts on soil microbial communities and ecosystem functions,” Frontiers in microbiology, vol. 9, p. 819, 2018.

[95] M. Niaounakis, Biopolymers: applications and trends. William Andrew, 2015.