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Microbial Production of Polyhydroxyalkonates (Bioplastic) using Cheap Household Waste Resources and Their Biomedical Applications: A Systematic Review

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Abstract: Plastics, micro-, and nanoplastics are widely distributed in the environment; soil, fresh, and aquatic water sources pose a great challenge to human health and well-being due to improper disposal, slow degradation, lack of effective recycling, and poor management. Contaminations associated with plastics and plastic products are more prevalent worldwide. To overcome the biohazards of plastics, an alternative to plastics is warranted. Bioplastics are a good replacement for synthetic plastic polymers. Several microbes are explored for bioplastic production, and genetic engineering techniques are used to modify the isolate to produce more PHA. To overcome the production cost involved in bioplastic production, cheap household wastes are extensively used to make a variety of polyhydroxyalkonates (PHA) based bioplastics. PHA and polyhydroxybutyrates (PHB) form a part of biomaterials that finds extensive biomedical applications, including tissue repair, regenerative medicine, wound healing, cartilage regeneration, artificial blood vessels, heart valves, and nerve conduits. It is also used in organ reconstruction, including scaffold making, bone implant, implant coatings, and sheath making. It also finds application in drug delivery, cancer treatment, and stem cell engineering. Most of the applications required in-depth in vivo studies to be used for human health care applications.

Keywords: polyhydroxyalkonates; polyhydroxybutyrates; bioplastics; tissue engineering; organ reconstruction; drug carrier; nanocomposites.

1. Introduction

Huge manufacturing costs hamper the large-scale production of PHA compared to synthetic plastics. Carbon sources and fermentation processes together contribute to the cost of PHA. Hence, identifying less expensive carbon sources, such as agricultural and industrial wastes, minimizes the PHA manufacturing cost and is a commercially viable option [1]. Currently, the major challenge is the PHA production cost from fossil-based polymers. For large scale production of PHAs requires sugar-rich substrates and pure or recombinant bacterial strains, which contribute to increased production cost [2]. Hence, looking for cheaper alternatives as feedstock for bacterial strains to produce quality PHAs with high yields is the current priority for the researchers. Using domestic waste as a feedstock for PHA production is advantageous for the effective management and disposal of waste generated. It is an environmentally friendly process that is also helpful in controlling environmental pollution.

The blended forms of PHA, including PHB and polyhydroxy butyrate-valerate (PHBV) are biodegradable, durable, thermostable, possess required strength, and are also toxic-free. PHA-based polymers are used in packaging materials for food storage, as hydrating agents and as additive for animal nutrients. The multifold use of PHA polymers in the medical field would certainly replace the presently used synthetic polymer-based materials.

2. PHA from Household Waste

The generation of household waste has increased immensely worldwide. Food waste from kitchens, restaurants, cafeterias, and the processing industry is the primary source of waste. It contains mostly rice, cocked meats, boiled vegetables, refined fruits, bakery items, and other dairy-based products. Food and Agriculture Organization (FAO) estimated that 1.3 billion tons of food products are wasted annually, including fruits, raw vegetables, dairy-based products, bakery items, and animal meat [3]. FAO and WRAP have taken a lot of initiatives for the effective use and reuse of food waste in the recent past [4]. Food waste consists of proteins, lipids, and carbohydrates-polysaccharides, including starch, cellulose, hemicelluloses, organic acids, polymers, and inorganic molecules [5]. Fermentable sugars are released from food waste by microorganisms, which serve as microbial feed for the synthesis of PHAs. Several products include biopolymers, nanocomposite materials, chitosan, corrosion resistors, enzymes for industrial use, films, organic acids, artificial pigments, silica, and biofuels like bioethanol, biobutanol, biodiesel, and biogas are produced by using PHAs as a cheap carbon source [6]. Pre-treatment is essential to ease hydrolysis and make food waste accessible to enzymatic degradation to increase PHA production. The appropriate pre-treatment method is essential depending on the fermentation broth, and bacterial strain used [7]. Simple pre-treatment methods such as acid hydrolysis and enzymatic degradation are often sufficient for household food wastes [8]. The chemical pre-treatment method is more advantageous for increased PHA production among the physical, chemical, and biological methods.

3. PHA Production from Fruits and Vegetable Wastes

Fruits and vegetable wastes served as good carbon sources for PHA production [9, 10]. Recently *Zobellela tiwanensis* strain DD5 converted banana peels into PHB production [11]. *H. mediterranei* DSM1411 utilizes date waste for PHBV production [12]. PHA is produced by *Pichia kudriavzevii* using banana peels as a carbon source and hydrolysates of the chicken feather as a nitrogen source [13]. *Bacillus halotolerans* produced 83% of PHA using pomegranate peels compared to *Cupriavidus necator* produced 71% of PHA [14]. The mcl-PHA is synthesized by fermentation process from waste frying oil by using *P. resinovorans* [15] and PHB production by *C. necator* [16]. PHA is also produced by *Pseudomonas alcaligenes* using food waste oil and simultaneous energy recovery [17]. Waste cooking oil or fish oil is also used as a cheap carbon source for producing PHB using *Cupriavidus necator* H16 [18].

4. Spent Coffee Grounds (SCGs)

Spent coffee grounds (SCGs) are also used as a cheap carbon source for producing PHA. Researchers use SCG hydrolysates to produce PHA by *B. cepacia* [19]. Halophile strain *Halomonas* is used to produce PHA from SCG hydrolysates after the chemical pre-treat process

[20]. It has been reported that the synthesis of PHA, biopolymer precursors, and polymer composite production from valorized SCGs [21]. PHA is also synthesized from municipal organic solid waste (OFMSW) [22]. Recently PHBV was produced from wheat starch wastewater (WSW) using (*B. cereus*) [23].

Burkholderia sp. F24 is used for producing PHA from sugarcane bagasse [24]. Sugar cane bagasse, maize cob, teff straw, and banana peel are used to produce PHB using *Bacillus* spp. [25]). PHA is also produced from rice husk by alkali treatment followed by enzyme hydrolysis with the help of *Burkholderia cepacian USM* [26]. PHB production from pineapple waste using *C. necator* A-04 has already been reported [27]. *H. mediterranei* is also used to produce industrial-scale PHA from cheese whey [28].

5. Production of PHB from Chicken Feather

Chicken feather is used as a substrate for the bacteria to produce PHBs. *Pseudomonas aeruginosa* (NCBI accession MF18889) isolated from the chicken (feather) waste disposal site in Namakkal, Tamil Nadu, India, produced 4.8 g/L of PHB under optimized conditions using chicken feather waste (15.96 g/L), at 37 °C temperature, and 6.85pH [29].

6. Other Cheap carbon sources for PHA production

Mannose, maltose, sucrose, pre-treated agricultural and industrial effluents (dairy, paper mill, sugarcane molasses), pineapple juice, cane molasses, glycerol waste, sugarcane bagasse, rice husks and corn cobs, date seeds oil, vegetable oil, sunflower oil, beer brewery wastewater containing maltose, cheese whey, teff straw, banana peel, discarded egg yolk biodiesel liquid waste (BLW), fructose and avocado oil, apple peel, pineapple peel, mango peel, waste paper hydrolysate, sugarcane vinasse and molasses, corn bran, wheat bran, rice bran, dairy waste B, rubber seed oil, waste cooking oil, tuna condensate waste from the canning industry and cassava peel waste are used as cheap carbon sources for PHA production [30].

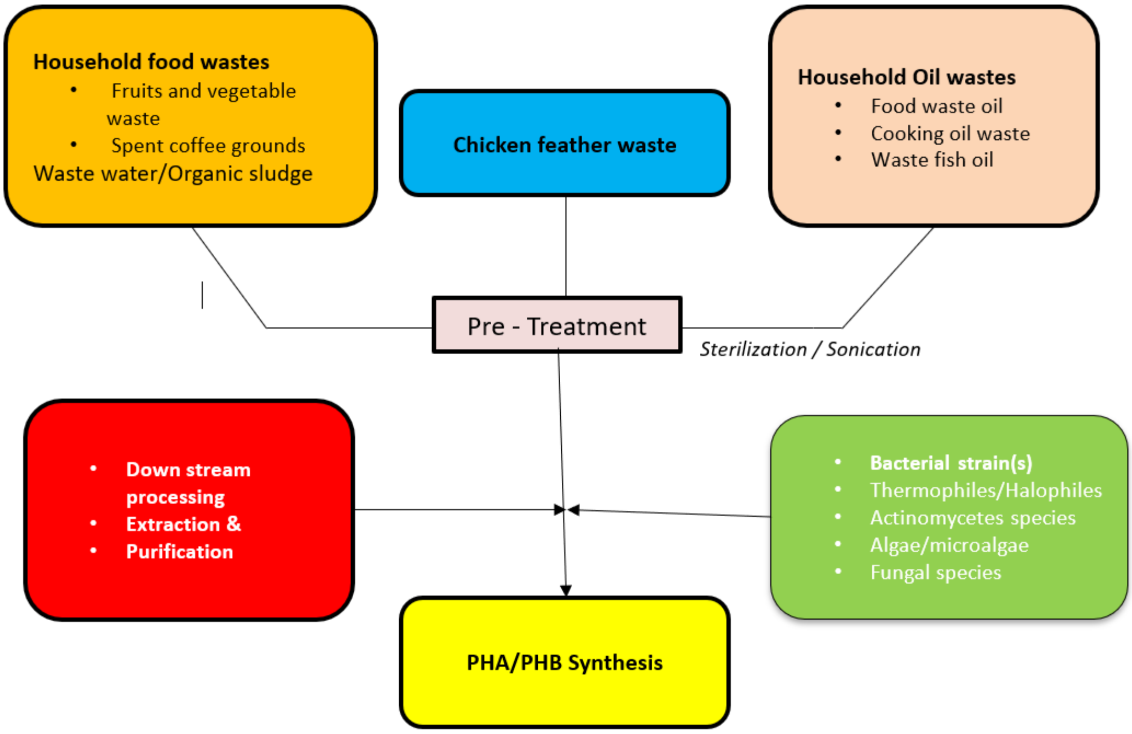

Figure 1. Microbial production of PHA/PHB from different household wastes.

PHA is also produced from various oils, including used cooking oil, wastewater with ground oil, soy oil, coconut oil, olive oil distillate, canola oil, palm oil, palm olein, and linear olefins [31]. *Cupriavidus necator* ATCC 17,699 produced *mcl*-PHA (90%) using canola oil as a substrate [32].

Several bacterial species, *Alcaligenes latus, Azobacter vinelandii, Bacillus megaterium, Cupriavidus necator*, *Pseudomonas oleovorans*, and *Escherischia coli*) are used for PHA production [33]. Other bacterial species include *Cupriavidus necator, Alcaligenes eutrophus, Wautersia eutropha*, *Ralstonia eutropha*, *Alcaligenes latus*, *Aeromonas hydrophila*, and *Pseudomonas putida*, uses agro-industrial residues as a carbon source for PHA production. *Acinetobacter junii* produces 94.3% PHB using rice milling as a substrate [34].

PHAs are accumulated as intracellular granules (storage compounds) in microbial cells. Several prokaryotes, including halophiles and thermophiles, are known for PHA production [35]. The process involved in the microbial production of PHA/PHB is shown in Figure 1.

Several halophiles have been reported to produce a variety of PHAs, including *Bacillus megaterium uyuni* S29, *Salinivibrio* sp. M318, *Salinivibrio* sp. TGB10, *Yangia* sp. ND199, *Halomonas venusta* KT832796, *Halomonas profundus*, *Halomonas pacifica* ASL10, *Halomonas salifodiane* ASL11, *Halomonas* sp.YLGW01, *Halomonas halophila*, *Halomonas hydrothermalis*, *Halomonas neptunia*, *Halomonas organivorans*, *Halomonas elongata* 2FF, *Halomonas bluephagenensis*, *Haloferax mediterranei*, *Haloteringena hispanica*, *Halopiger aswanensis*, *Halogranum amylolyticum*, *Halogeometricum borinquense* strain E3 and *Natrinema ajinwuensis* [35].

7. PHA-Producing Bacteria

7.1. Thermophiles.

Several thermophilic bacteria capable of producing a variety PHAs have been listed here. *Amphiplicatus metriothermophilus, Aneurinibacillus danicus, Aneurinibacillus terranovensis, Aneurinibacillus thermoaerophilus, Anoxybacillus calidus, Anoxybacillus vitaminiphilus, Aquabacterium tepidiphilum, Bacillus thermoamylovorans, Caldimonas manganoxidans, Caldimonas taiwanensis, Chelatococcus daeguensis, Chelatococcus thermostalatus, Cupriavidus sp., Dichotomicrobium thermohalophilum, Elioraea tepidiphila, Elioraea thermophile, Geobacillus kaustophilus, Geobacillus stearothermophilus, Hydrogenophilus thermoluteolus, Inmirania thermothiophila, Pseudomonas sp. SG4502, Pseudonocardia thermophile, Rubellimicrobium thermophilum, Rubrobacter spartanus, Rubrobacter xylanophilus, Schlegelella aquatic, Schlegelella thermodepolymerans, Synechococcus sp. MA19, Tepidicella baoligensis, Tepidicella xavieri, Tepidimonas alkaliphilus, Tepidimonas aquatic, Tepidimonas fonticaldi, Tepidimonas charontis, Tepidimonas ignava, Tepidimonas sediminis, Tepidimonas taiwanensis, Tepidimonas thermarum, Tepidiphilus margaritifer, Tepidiphilus succinatimandens, Tepidiphilus thermophiles, Thauera hydrothermalis, Thermomonas hydrothermalis, Thermosyntropha lipolytica, Thermus thermophiles, Ureibacillus terrenus, Ureibacillus thermophiles and Zhizhongheella caldifontis* [35].

7.2. PHA production by algae.

Aulosira fertilissima, Botryococcus braunii, Microalgae consortium, Nostoc muscorum, Spirulina sp., Synechococcus elongates, Synechococcus subsalsus, and

Synechocystis salina. Among them, Nostoc muscorum produces PHA (69 % yield) under phosphorus deficiency [36].

8. Applications of PHA

PHA/ PHB are extensively explored for industrial and medical applications. Commercially available PHAs produced by different companies worldwide and their applications are given in Table 1. Multiple applications of PHAs/ PHBs and their nanocomposites are schematically shown in Figure 2. PHA is used in bone scaffolds, tissue engineering, soft tissues, and organ reconstruction. The elasticity and brittleness of the biopolymer are controlled by blending techniques. Biomedical applications of PHA include drug carriers, bone implants, tissue engineering, tissue scaffolds, and the development of artificial organ constructs. PHA synthesized from Gram-positive bacterial strains is non-immunogenic due to the lack of lipopolysaccharide layer and is medically more biocompatible [37]. PHB, PHBV, poly(3-hydroxybutyrate-co-3-hydroxyvalerate-co-3- hydroxyhexanoate) PHBHHx are widely used as bioplastic biomaterials. To control autoimmune diseases, PHBHHx was used as an immunosuppressant drug carrier [38, 39]. PHBV composite material is used for bone regeneration, and moreover, it is biocompatible with blood tissue. PHBV is also used in tissue engineering for the adhesion, attachment, and growth of fibroblasts [39, 40]. PHB fibers are used to manufacture biocompatible sutures (Phantom Fiber^{TM}), surgical mesh (TornierV), and scaffold (BioFiber^{TM}) marketed by Tornier Co. Braun Surgical Co. also manufactures sutures (MonoMax^{R}), Tepha Inc (TephaFLEX) [41] and Galatea Corp. manufactures GalaFLEX mesh [41].

Table 1. Commercially available PHAs produced by companies and their applications.

PHA Brand Name	Company, Country	Year	Applications
Biopol	Yield10 Bioscience, USA	Since 1990	Fabric and film production, food industry (cups, plates), and disposable items (razors, rubbish bags)
Biomer	Biomer, Germany	Since 1994/1995	Cardiovascular applications, in blood contact applications (tissue engineering scaffolds)
Biocycle ®	PHB Industrial S.A., Brazil	Since 2000	Fibers, coating paper and cosmetic packaging, Plastic sheet films, and injection
Mirel™	Yield10 Bioscience, USA	Since 2006	Injection molding, commodity applications, shampoo and cosmetic bottles, cups and food containers, cosmetics micro-powder, and plasticizers
MINERV-PHA™	Bio-On, Italy	Since 2007	Cosmetics, packaging, automotive and electronics, food pack, fibers, and toys
Nodex™	MHG, Bio, USA	Since 2007	Mulch, bags, bottles, packaging, laminates, coatings, and non-woven fibers
TephaFLEX™	Tepha, USA	Since 2007	Surgical film, mesh, sutures, films, and textile products
Enmat™	TianAn Biopolymer, China	Since 2007	Plastic fibers, non-wovens, thermoplastics, films, sheets, bars, rods, powder, mulching films, and rubber packaging materials
Ecomann®	Shenzhen Ecomann Biotechnology Co., China	Since 2008	Packaging, paper coatings, cosmetics, personal care, and footwear
Seluma™	Danimer Scientific, Georgia	Since 2008	PHA resins, utensils - cups, lids, straws, bottles, and composite bags
AONILEX®	Kaneka Corporation, Japan	Since 2011	PHB pellets increase the strength and tear resistance of packaging films, composite bags, mulch films, electronics, and automotive
Hydal	Nafigate Corporation, Czech Republic	Since 2011	PHB from waste cooking oil, coconut peeling milk with PHB, sunscreen with PHB for UV protection

PHA Brand Name	Company, Country	Year	Applications
AirCarbon™	Newlight Technologies, USA	Since 2013	Cosmetic packaging, films, sheets, coatings, and injection molding purpose
WersaMer™	Polyferm, Canada	Since 2013	Packaging, coatings, paints, adhesives, plastic additives, inks, toners, thermo-elastomers, and medical applications
BIOFASE	Biofase, Mexico	Since 2014	Straws and cutlery
EastmanTREVA	Eastman Company, USA	2017	Cosmetic packaging materials

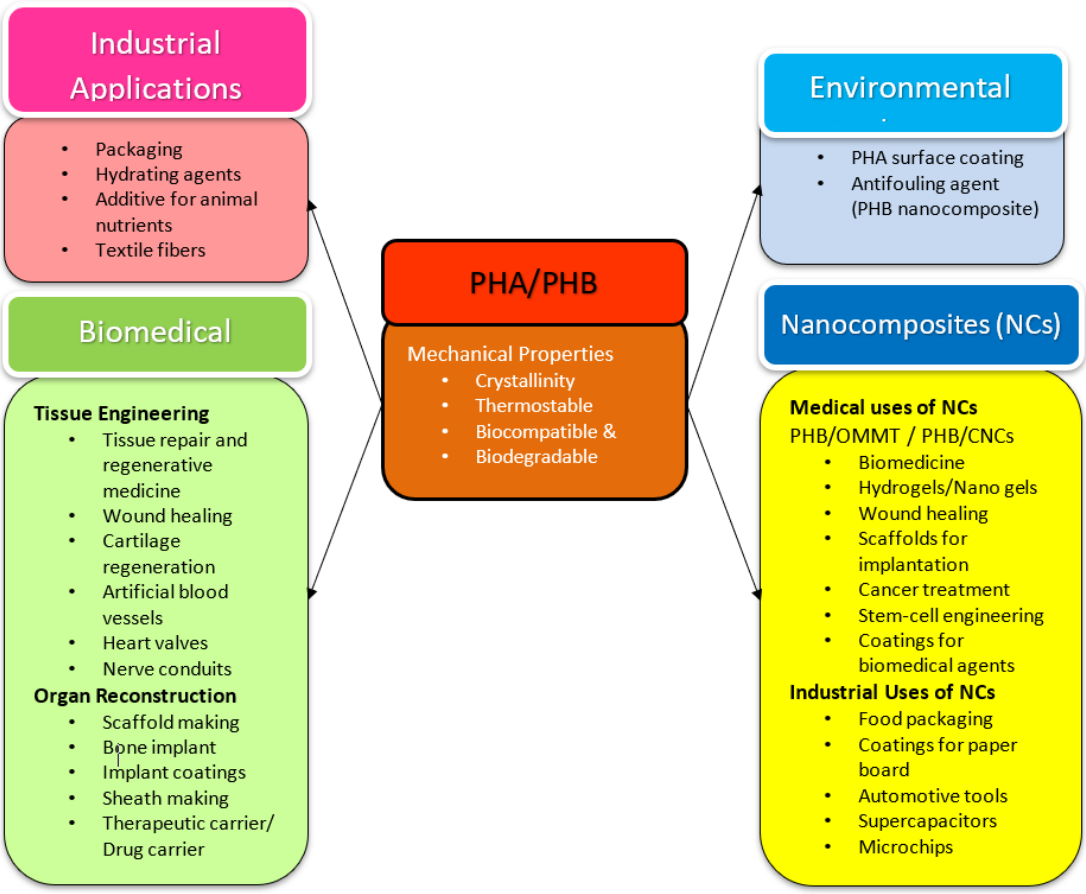

Figure 2. Applications of bioplastics (PHA/PHB) and its nanocomposites.

8.1. Soft tissue repair and regenerative medicine.

PHAs are used for soft tissue engineering and the fabrication of tissue and bone scaffolds. Making bioactive glasses (BGs) and introducing other inorganic chemicals are in progress to increase the bioactivity of PHA. [42]. PHAs are used for tissue regeneration due to their biostability, mechanical characteristics, and minimal tissue-associated hazards [43]. PHAs attach to cells, cause no hindrance to cell proliferation, and possess the required mechanical strength for the regeneration of the tissues [44]. Scaffolds created using PHAs serve as biomimetics, imitating the targeted tissue and encouraging cell growth and differentiation [45]. PHAs used in tissue regeneration and cell line cultivation for tissue culture have not shown any toxicity after human implantation [46]. Biomaterial scaffolds prepared with collagen, chitosan, hyaluronic acid, gelatin, alginate, agarose, and fibrin are used along with PHA for repairing spinal cord injury [47].

8.2. PHA and Wound healing.

Natural polymers such as collagen, chitosan, fucoidan, hyaluronic acid, and synthetic polymers (polyurethanes and Teflon) are used for the artificial dressing of wounds [48].

Engineered nanostructures were used to create an antibiotic cover over the wound and inhibit the biofilm formation by the pathogenic bacteria, thereby improving the wound healing process [48]. The PHA-based biopolymer improves wound-healing, reduces inflammation, and increases skin angiogenesis [45]. Pathogens degrade the PHA shells loaded with biocides are destroyed themselves [47].

8.3. Bone tissue engineering.

Reconstruction of new bone in bone tissue engineering with the help of natural or synthetic mechanical support (PHB as a bone scaffold) increases cell growth [48]. Enhanced compressibility and elasticity were achieved by mixing with hydroxyapatite (HAP), and hydrogel- PHB supports osteoblast feedback [49]. Porous and biodegradable scaffolds are produced by using PHA and HA mixture for the regeneration of bone matrix [50]. Piezoelectrical scaffolds are made by blending mineralized $CaCO_3$ with PHBV, and the resultant biocomposite film also offers biodegradability and bone regeneration [51].

8.4. Regeneration of articular cartilage.

Biopolymer scaffolds, PHB, and poly(3-hydroxyoctanoate) (P_3HO) have been used to repair bone cartilage and decrease the risk of secondary osteoarthritis growth. It is achieved by mixing these polymers in different combinations by controlling certain mechanical properties and ultra-structure [52]. Cartilage tissue engineering by PHB/chitosan scaffolds with the addition of alumina nanowires (3%) showed enhanced compressibility [53].

8.5. Liver tissue engineering.

Poly(3-hydroxybutyrate-3-hydroxyvalerate-co-3-hydroxyhexanoate) PHBVHHx and de-cellularised liver scaffolds are the two recently developed scaffolds for liver tissue engineering. To mimic the natural extracellular matrix, glycosaminoglycans, laminin, type I collagen, and fibronectin are added in exact proportions to maintain the diversity of growth factors, oxygen supply, and cell nourishment are not affected when blood vessels are kept intact [54].

8.6. Cartilage tissue repairing.

The scaffold developed by mixing PHAs, poly (3-hydroxyoctanoate) and poly (3-hydroxybutyrate), is very effective for cartilage repair. Making scaffolds by the copolymerization method has been reported to be effective in increasing the melting temperature of PHAs [55]. Mixing poly (3-hydroxybutyrate) and poly (E-caprolactone) with silica is used to construct 3D scaffolds from electrospun fibers. The resultant scaffolds possess increased strength and stiffness without any effect on attachment and cell viability [56].

8.7. Blood vessels and heart valves.

P3HB4HB is extensively used to construct blood vessels due to its elasticity and elastin formation [46]. In an experimental sheep model, the pulmonary artery was inserted with aortic valves, PHBHHx-coated hybrid valves. PHBHHx coating increases Young’s modulus and tensile strength and also reduces the calcification process. This hybrid valve resembles the original valve and is used as a replacement for the original valve tissue [57].

8.8. Nerve conduits.

In the past, many biological and chemical agents are used for nerve regeneration. A nerve conduit made up of PHB coated with chitosan is used to carry human bone marrow Mesenchymal stem cells to repair nerve injury in animal studies [58]. PHA-graft-graphene biomaterial is also used to prepare nerve conduits, implants, and biosensors due to its high electrical conductivity [59] and low critical filing content [60]. A hybrid nanocomposite-based electrochemical biosensor PHA/AuNPs/ HRP/ITO is used to detect artemisinin in body fluids [61].

8.9. Drug carriers.

PHA-derived engineered nanoparticles, microcapsules, and microspheres were developed for medical applications [63]. MCL-PHA amphiphilic copolymer is used for drug delivery [62]. Desired hydrophobicity, porosity, and crystallinity of SCL-PHA make them very specific as drug carriers and the release of drugs without affecting the carrier [141]. PHA-based nanoparticles and microbeads are used as drug (therapeutic agents) carriers [64]. Gentamicin sulfate, simvastatin, and ciprofloxacin are delivered by using PHA-based drug carriers [45].

8.10. Antibiotics delivery and Biodegradable PHA rods.

Polymers of PHA are extensively used for the encapsulation and delivery of antibiotics. Antibiotics rifampicin and tetracycline are delivered by using PHA microspheres. This drug release rate can be controlled by polymer crystallinity; at higher polymer crystallinity, the release rate is lower [65]. Antibiotics-loaded PHA rods are used to treat osteomyelitis [47].

8.11. Organ reconstruction.

PGA non-woven fibers are used to replace the dog esophagus, and keratinocytes and fibroblasts are seeded in the prostheses and used in situ. The esophageal substitution of prosthesis has led to muscular membrane development [66]. Poly (3HB-co-3HV) and poly(3HB) are used to repair and reconstruct the urethra. Dogs' urethra is also substituted by entwined laces of poly (3HB) coated with PHBV [67]. P3HB is safe for urethra replacement and used in the reconstruction and repair of tissues in experimental animals [68].

8.12. Bone tissue engineering.

Due to its vascularity and degradability, PHA can be used in making bone scaffolds [69]. By introducing hydroxyapatite (HA), osteoconductivity and osteoinductivity can be incorporated into a bone scaffold. Studies using MC3T3- E1 mouse pre-osteoblast cells showed that PHB/HA porous blends are stable and biocompatible with cell adhesion and proliferation for bone tissue regeneration [70]. Different agents of varied atomic sizes were used to adjust the porosity and the interconnectivity between the particles in scaffolds by solvent-casting particulate leaching (SCPL) technique [71]. Fabricating PHA-PEG scaffolds using sodium chloride and PEG as porogen's using SCPL results in PHA-PEG scaffolds with homogeneous pore sizes of 378–435µm with increased water retention and absorptivity[71]. Nanofibrils obtained from electrospinning possess sufficient porosity, structural stability, compatibility, and matching with the targeted tissue. Electrospun fibers are similar to cellular architecture and can regulate the infiltration and viability of cells [72]. Biomaterials such as PHAs, cellulose, chitin, HA, PEG, PLA, etc., have been explored for mouse cranium bone regeneration [73].

8.13. PHA-based implants and implant coatings.

PHAs are bio-compatible and tissue-compatible, used in various implants, and reported to trigger cell proliferation and growth. It is non-carcinogenic when used in bioimplants and scaffolds [46]. The oligomeric and monomeric forms of biodegradable products derived from PHA are non-toxic to cells and tissues. The PHB-based pericardial scaffold was used successfully in sheep as a tissue implant [74].

9. PHA Nanocomposites

PHB/OMMT (organically modified montmorillonite) nanocomposites are used for bone tissue engineering due to their porosity, non-immunogenic property, and biocompatibility. It is also used for 3D organ bioprinting and lab-on-a-chip scaffold engineering applications [75]. PHB/CNCs (cellulose nanocrystals) nanocomposites find application in medical and packaging industries. The production cost of PHB/CNCs is less due to CNCs from cheap natural resources. Presence CNCs increase their biodegradability when used for packaging. PLA/PHB/CNCs containing carvacrol are used for packaging [76]. It also showed better disintegration within 17 days during composting. PHB/CNCs nanocomposites are often prepared with plasticizers for biodegradable packaging material. PHB/CNCs nanocomposites are also used as paperboard coatings, which increases mechanical strength and protects from moisture [77]. In vitro studies showed that PHB/CNCs nanocomposites are safe without toxicity for human applications. The possibility of using PHB/CNCs nanocomposites in drug or fertilizer encapsulation is also viable [78].

10. Conclusions and Future Prospectives

Many bacterial species produce PHAs/ PHBs; recently, researchers have reported the production of PHA/PHB by submerged fermentation of *Paraburkholderia* sp. PFN 29 [79]. PHA, its homopolymers, and copolymers are extensively used in industry and the medical field. PHA biopolymer is used for tissue engineering (scaffolds for tissue/organ reconstruction and substitutes bone tissue) and regeneration, drug delivery, plasmid DNA delivery, and chemotherapeutics due to its high biocompatibility, bioactivity, and versatility. PHA is also used in biosensors and electronics as well. PHA-based nanomaterial would be used as a packaging agent for hormones, drugs, and antibiotics. High PHA-yielding and fast-growing microbes need to be identified under optimized cultural conditions. The properties and quality of PHA are improved to make it a suitable biocomposite material for biomimicking and to replace its synthetic counterparts. PHA, PHB, and PHBHHx would be the ideal candidate for next-generation bioplastics to replace synthetic petroleum-based polymers to reduce pollution and improve the ecosystem and human health.

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Conflicts of Interest

The authors declare no conflict of interest.

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