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Review Article

THE PROMISES OF THE POTENTIAL USES OF POLYMER BIOMATERIALS IN BIOMEDICAL APPLICATIONS AND THEIR CHALLENGES

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ABSTRACT

Biopolymers are a prominent class of functional materials ideal for high-value applications, and they fascinate researchers and experts from various fields. Polymers are flexible building blocks in many chemical combinations and blend to create composite materials with complementary qualities. The biomedical use of polymeric biomaterials was analyzed scientifically and technologically in this study, along with a compilation of their uses, manufacture, mechanical qualities, and key characteristics for the biomedical sector. The volume of scholarly publications and patents demonstrates the current knowledge of polymeric biomaterials. These biomaterials may now supplement, strengthen, or perform a particular role in the human body. Immune reactions persist due to the complexity of biological systems, impeding the growth of tissues and functioning organs in a laboratory setting.

Keywords: Biomaterials, Synthetics polymers, Biomedical applications, Challenges

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INTRODUCTION

Biopolymers synthesized by organisms naturally fulfill various biological functions, such as the preservation of genetic material (nucleic acids), cell stability and metabolism (proteins), and energy storage (polysaccharides). The diverse materials with particular physicochemical properties allow them to be used by different sectors, including health, food, pharmaceuticals, and plastic [1, 2]. They can also be obtained from plants or synthetic biology. Biopolymers have advantages compared to fossil polymers, such as great diversity in mechanical and physical characteristics, degradability, and recyclability, which determine their use. Its industrial use is wide and includes biomedical materials, food packaging, cosmetics, food additives, fabrics, plastics for industrial use, absorbents, biosensors, and data storage devices. The characteristics of biopolymers, such as biodegradability and hypoallergenicity, facilitate their use in medical practice, making them excellent materials for manufacturing implants to replace damaged organs and structures [3]. Several biopolymers have been used in medicine to prepare implants to repair and replace bones [4, 5] and heart valves [6].

Among the various existing biopolymers, biodegradable polyester polymers are among the most commonly used in manufacturing medical devices, particularly those derived from polylactic acid (PLA), polylactic-co-glycolic acid (PLGA), polyglycolic acid (PGA), poly-ε-caprolactone (PCL), poly-3-hydroxybutyrate (or poly-β-hydroxybutyric acid, P3HB), poly-4-hydroxybutyrate (P4HB), poly(3-hydroxybutyrate-co-3-hydroxyvalerate) (PHBV), poly(propylene carbonate) (PPC), poly(butylene succinate) (PBS), and poly(propylene fumarate) (PPF). Of these, hundreds of products can be found already available, and each year, new products are introduced in the market, duly supported in the aspects of biocompatibility and in their mechanical characteristics, which, together, allow a high degree of modification and selectivity for the production of medical articles. Still, with the scientific advances of the last decades, several blends and modifications in their structure and composition circumvented their main adverse attributes, such as hydrophobicity and low cell adhesion [7-10]. The current market, which includes surgeries with regenerative implants, cell therapies, and tissue repair, is approximately 23 billion dollars per year, projected to reach 94.2 billion dollars by 2025. In this context, bioresorbable polyester polymers are considered the most competitive due to the cost-effectiveness of their production and the reproducibility of the synthesis, modification, and manufacturing techniques of these and their derivatives. In addition to the described biological characteristics, the physicochemical characteristics of such polyesters allow their use in the manufacture of sutures, screws, controlled drug delivery vehicles, and implantable devices [4, 7, 11].

Polyesters act as inert supports and/or vehicles for the controlled release of drugs in currently available implantable devices [12]. Polymers for biological applications are constantly modified to acquire desirable characteristics, such as endothelial adhesion, hydrophilicity, and inability to activate the immune response and/or coagulation. Therefore, substantial scientific research has been conducted to give polyesters specific characteristics different from those already commercially available [13, 14].

This paper was documented to offer insights into the promises and difficulties of the usage of polymeric biomaterials in biomedical applications gathered from 2010 to 2022. An analysis of the immune responses to some materials treated in this review is presented. In addition, the applications of polyester biopolymers, PLA and P4HB, in biomedical applications are also highlighted. The classification of biopolymers is shown in fig. 1.

Biopolymers

Biodegradable polymers produced by living organisms are known as biopolymers. This definition is one of several proposed for the term biomaterial. Biocompatibility is the primary requirement for any material to be considered a biomaterial [15]. Biomaterials may be categorized into four categories based on their chemical makeup: metals, ceramics, polymers, and composites. Dental implants, hip and knee replacements, bone plates and pins, and other hard tissue fixation devices made of metals (e. g., titanium, stainless steel, silver [17], gold, and cobalt-chromium) are examples of biomedical applications. Certain metal alloys may play more dynamic functions, such as those in cardiovascular stents and heart valves or maxillofacial orthodontic arches [16]. Ceramics (e. g., calcium phosphates, bioactive glasses, porcelain, carbons, and alumina) are frequently used as surface coatings to cover dental and orthopedic implants to reduce wear [16, 17]. Ceramics are also extremely biocompatible and inert materials, with great hardness and resilience to compression. Solids that mix components (such as polymers, ceramics, or metals) to improve each other's mechanical properties are called composites (e. g., hydroxyapatite-collagen, polyvinyl chloride-glass fillers), which differ from the characteristics of homogeneous biomaterials. Hence, they may be used in dental restorations [16]. There is no denying the increasing prominence of polymers in the biomedical and pharmaceutical industries in recent years. Recent biomedical studies have focused on developing biomaterials with mechanical characteristics amenable to body movement with limited shelf life.

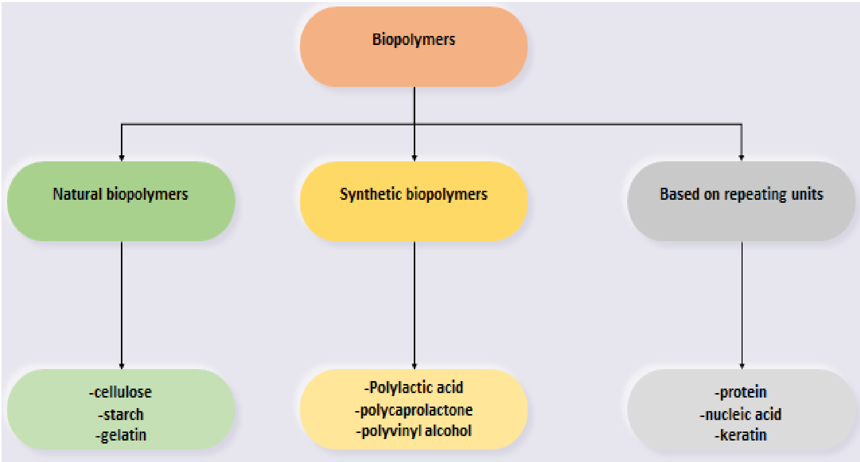

Fig. 1: **Classification of biopolymers (Source: author)**

Synthesis of PLA

PLA is an aliphatic, thermoplastic, semi-crystalline, or amorphous polyester, biocompatible and biodegradable, synthesized from lactic acid obtained through carbohydrate fermentation. It has gained commercial interest in textile applications due to its properties being similar to those of polyester, one of the most used polymers in the textile industry, and being biodegradable and obtainable from renewable sources, which are its great advantage [18]. This polymer was discovered in 1932 by Carothers (Dupont), who produced a low-molecular-weight material by heating lactic acid under a vacuum. However, its initial uses were limited to medical and pharmaceutical applications due to its low availability, high manufacturing cost, and low molecular weight [19]. Due to its biodegradability and biocompatibility, this polymer has become one of the main materials of interest in the biomedical area. The recent technological advances in dextrose fermentation, obtained mainly from corn, rice, potatoes, beets, wheat, and agricultural residues, drastically reduced the cost of producing lactic acid, heightening the interest in the precursor monomer for the production of PLA [20]. Biologically synthesized lactic acid almost exclusively produces L-lactic acid, producing L-polylactic acid (PLLA). In contrast, the chemical process leads to different L-and D-lactic acid rates, resulting in varied PLLA and D-polylactic acid (PDLA) rates. Currently, lactic acid industrial production depends on the microbial fermentation of carbohydrates, a more economically viable process than the chemical route, which produces a high degree of pure lactic acid in addition to the production of various rates of PLLA and PDLA [18, 20, 21].

The first step in the biological process of making PLA is to turn plant-based polysaccharides into glucose. Next, lactic acid is made by fermenting glucose, which turns glucose into lactides when certain catalysts are present. Lactide, a ring formed from lactic acid dimers, is used to produce high-molecular-weight PLA in the ring-opening polymerization route and, therefore, is an important intermediate in the industrial production of PLA [18]. Due to the chiral nature of lactic acid, lactides exist in two main forms: L and D-lactide. By the synthetic route, after purification by vacuum distillation, the lactide is converted into the PLA polymer through polymerization in the presence of an appropriate catalyst. After conversion, two types of PLA are obtained: PLLA (low molecular weight) and PDLA (high molecular weight, fig. 2) [20, 22, 23].

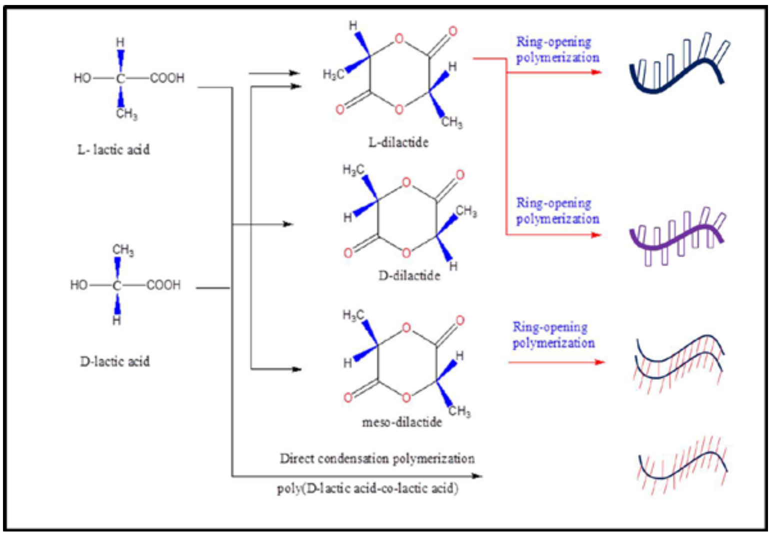

Fig. 2: Synthesis of (PLA) with high molecular [20]

Biomedical uses of PLA

In recent years, the development of biomaterials has become the focus of academic and industrial interest. Biodegradable polymers gained great importance with the discovery of their usability in biomedical applications. One of the most common commercially biodegradable polymers is PLA. Because of its biodegradability and biocompatibility in the human body, PLA has piqued the interest as a potential material for medical applications. The production of tissue-engineering scaffolds, delivery system materials, membrane covers, various bioabsorbable medical implants, and sutures used in dermatology and cosmetics have all utilized PLA [24-27]. The range of applications for PLA is so broad that a single polymer can be made usable for several purposes by making minor adjustments in the organization of its physical and chemical structures. The polymer can often be blended or copolymerized with other polymeric or nonpolymeric components to produce the required behavior. Meanwhile, for applications, particularly those involving biocompatibility, the surface qualities of materials play a pivotal role in determining their various applications. Many surface modification tactics, such as physical, plasma, chemical, and radiation-induced approaches, have been utilized to develop PLA biomaterials with appropriate surface properties [28-30]. The following sections provide a concise overview of the current state of PLA mixes in tissue engineering, drug delivery, wound treatment, implant creation, and biomaterial research for future applications in the medical field (fig. 3).

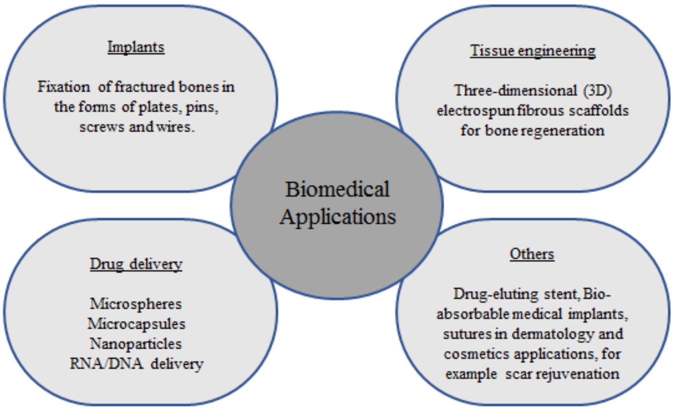

Fig. 3: Biomedical applications of PLA synthesis of P4HB (Source: author)

P4HB is a resorbable thermoplastic polyester belonging to the class of polyhydroxyalkanoates (PHA), which are produced by microorganisms. This polymer has a molecular structure similar to PGA and PCL, both synthetic resorbable polymers, differing only in the number of methylene groups in its structure (fig. 2). P4HB can be synthesized through a fermentation process by recombinant *Escherichia coli* K12 bacteria, but due to its difficult chemical synthesis. After fermentation, the polymer is isolated and purified, resulting in a product of high purity that can be used for the production of various devices with medical applications [31, 32].

The production of P4HB fibers through spinning by a fusion process resulted in monofilament and multifilament. According to the author, an alternative to the melting process is processing a solution containing polar organic solvents. When designed with specific guidelines, its fiber structure demonstrates high resistance and provides a complex with better mechanical properties, such as tensile strength and elasticity. P4HB stands out from other materials composed of PLA and PGA because it is ductile and not susceptible to brittle fractures. The plastic material, under the action of traction forces, undergoes a certain degree of stretching under conditions of overload without fragmentation or damage to the device and has greater tensile strength than PCL [33, 34].

P4HB demonstrates excellent biocompatibility, and the Food and Drug Administration (FDA) approved its initial use in 2007 when applied to a monofilament for soft tissue sutures and ligatures [33]. Subsequently, it was used to construct surgical meshes for repairing hernias, tendons, and ligaments and in plastic and reconstructive surgery. Many studies analyze the advantages of its use in cardiovascular medicine in stents, vascular grafts, and heart valves [34]. *In vivo* studies demonstrate that its resorption probably occurs from intense enzymatic hydrolysis, which causes erosion of the surface of the device and may influence its capacity for mechanical resistance. It has varying total resorption time according to the size and the order of the fibers; hence, the greater the order, the longer the process will be. In general, a total resorption period of 12 to 18 mo is estimated. 4-hydroxybutyrate (4HB) is obtained as a product naturally found in mammals, present in organs such as the heart, brain, and lungs. This compound is quickly metabolized by the organism, being modified until it enters the Krebs cycle as acetyl-CoA. Due to oxidative metabolism, it is completely metabolized, having a half-life of approximately 27 min and not showing cytotoxicity [31, 34].

P4HB can be used in the development of devices for closing septal defects. Its first use for this purpose was in the development of a self-expanding device made of two P4HB structures and a cellularized P4HB-PGA membrane, allowing the development of a tissue with collagen for subsequent implantation. Positive results were obtained in both reports [33, 34]. P3HB, an isomer of P4HB, is not applicable in cardiovascular medicine because it induces extensive inflammatory responses in animal models.

Biomedical uses of (P4HB)

Although the first synthetic absorbable material was developed for medical uses in 1970, its rapid disintegration in the body and low strength retention *in vivo* have persisted ever since [35]. Aliphatic polyesters like P4HB are also produced by microorganisms under unstable growth conditions in less stable environments. Their potential use as biomaterials in medical devices and tissue engineering is intriguing due to their biodegradability and heat treatability [36]. Biodegradable polyester P4HB has been approved by the FDA for use in tendon and hernia repairs [34]. Previous studies have also shown that P4HB undergoes some degree of surface erosion during its degradation *in vivo* [33]. Reducing deterioration is recognized as crucial for host transformation. 30 It is also beneficial because the scaffold degrades at a rate that can be adjusted to coincide with the rate at which new tissue forms. Hence, P4HB has so many potential uses in the medical field [31]. A double-emulsion solvent-diffusion technique was utilized to create porous P4HB microspheres. Bone filler implants using open-porous P4HB microspheres were studied for their potential. Open-porosity P4HB microspheres were extensively investigated for their morphology, cell survival, and hemolysis [37]. Due to its unique characteristics, P4HB is recognized as a promising biodegradable and biocompatible biopolymer with immense potential in biomedical engineering. However, high production costs are still an obvious challenge faced by PHA research.

Biodegradable materials

Biodegradable materials are substances that can be broken down by natural processes into simpler compounds that do not harm the environment. They are typically made from natural sources, such as plant-based materials, and can be broken down by microorganisms (bacteria, fungi, and algae) [38]. Under typical environmental circumstances, these microbes break down organic materials through enzymatic activity. These plastics, known as biopolymers, are often produced by fermentation. The most well-known is PLA, made from maize or wheat starch. Through fermentation, starch is converted to lactic acid, a basic monomer polymerized chemically to become PLA [39]. Biopolymer applications are restricted to uses of extremely high value as pharmaceutical goods (sutures, materials for surgical packing), applications with a major ecological marketing component, and small-scale production at a high cost [40].

The phrase "biobased" refers to polymers made from renewable sources and focuses on the raw ingredients used. Raw resources might be considered renewable when they are replenished naturally at a pace equal to or greater than their use [41]. Biobased materials include carbon from a source that is thought to be renewable due to biological processes. Biodegradable plastic is a substance that degrades biologically and breaks down into carbon dioxide, water, inorganic compounds, and biomass at a comparable pace to other compostable materials while also leaving no recognizable residues or toxins behind [15].

Biodegradable polymers are widely used in medical applications. They can be used as surgical sutures and implants, eliminating the need for a second surgery to remove the implant at the end of its functional life. Biodegradable polymers can also be used as drug-delivery devices and tissue engineering scaffolds. They are biocompatible and can be broken down, excreted, or resorbed without removal or surgical revision. Biodegradable polymers can be designed to degrade at a specific rate, allowing for controlled drug release. Some specific examples of medical applications of biodegradable polymers include wound dressings, tissue engineering scaffolds, drug delivery systems, and orthopedic implants [19, 16, 17, 42].

Synthetic polymeric biomaterials

Synthetic polymers are the most versatile materials, and their use in biomedical applications includes contact lenses, pharmaceutical vehicles, dental materials, substrates for tissue engineering, and others [43]. Research should focus on developing biodegradable and/or bioabsorbable synthetic polymers that can decompose as tissue regeneration progresses, as is the case with polyacrylates, polysiloxanes, polyamides, polycarbonates, polyesters, polyurethanes, polystyrenes, synthetic polypeptides, polyalkenes, and polyols [44, 45].

Polyacrylates

Polyacrylates are a family of polymers that start with unsaturated carboxylic acids. Polyacrylates have a wide range of applications in biomedicine [45]. The most used polyacrylate in the world is polymethyl methacrylate (PMMA). PMMA is a transparent thermoplastic with a lower density than glass and high impact resistance. It has good biocompatibility with human tissues and is used to develop rigid intraocular lenses. It has been endorsed in orthopedics as an adhesive for bones, cranial prostheses, and bone repairs [45, 46]. Other PMMA applications also include its use as a vehicle for delivering genetic material, replacing viral vehicles [44].

Polysiloxanes

Polysiloxanes, also known as silicones, are made up of alternating oxygen and silicon chains with organic side groups. These biomaterials were the first inorganic polymers developed and have diverse applications due to their physicochemical, electrical, mechanical (elastomeric), and biocompatibility properties. Polysiloxanes comprise a large family of resins, oils, and gums. Polydimethylsiloxane (PDMS) stands out for biomedical applications [47]. PDMS is an odorless thermoset that does not support bacterial growth, is resistant to blood corrosion, and is permeable to oxygen. The polymer can be cross-linked, allowing its properties to mimic soft tissue such as mammary and maxillofacial implants, joints, catheters, pacemakers, and blood pumps [47].

One of the limitations of the use of PDMS is its hydrophobicity, which is why PDMS does not allow cell adhesion. Therefore, recent research focuses on modifying it superficially with gamma rays, plasma, lasers, corona treatments, and "grafting," to generate surfaces that allow cell adhesion [47, 48].

Synthetic polyamides

Polyamides are polymers with amide groups attached to aromatic, aliphatic, or both aromatic and aliphatic groups in the backbone of the polymer. Amides with benzene groups in their main chain are called aramids, whose main representative is Kevlar. Among the aliphatic polyamides, the most representative polymer is nylon, and of the semi-aromatics, trogamid. Because of their high degree of crystallinity and interchain hydrogen bonding, synthetic polyamides have good spinning characteristics, increasing their strength in the direction of the fiber. Applications of synthetic polyamides focus on the controlled release of drugs [3]. In these situations, natural biopolymers like chitosan reinforced with polyaramide are electrospun with nanoparticles to create nanomaterials. Sutures made from these biomaterials are commercially available [48].

Polycarbonates

Polycarbonates are a family of polymers with carbonate functional groups synthesized by ring-opening (R-O-C(=O)-O-R)′. Polycarbonates can be aromatic or aliphatic depending on the R and R′ substituents. Aliphatic polycarbonates (PAC) are biodegradable, easily hydrolyzed, and have a low physiological response than other materials [49]. The main application of PACs is biodegradable implants, which have the advantage of not requiring secondary surgery to remove the biomaterial. A functionalization or copolymerization with amino acids or bioactive substances (desaminotyrosine, L-tyrosine, antibiotics, and tyramine) is needed for the use of PAC [49-51].

Synthetic polyesters

Polyesters are polymers with ester groups in their main chain. They are created by ring-opening reactions, as in the case of PCL or condensation reactions. Some polyesters are biodegradable, as in the case of PCL. PCL has been investigated as a support for tissue engineering [52]. Additionally, this is a very versatile biomaterial and allows the design of nanofibers, nanospheres, foams, and other things for applications in orthopedic and maxillofacial surgery, controlled drug release systems, tissue reinforcement, sutures, nerve regeneration, etc. [52]. Another polymer that falls into this group is polyethylene terephthalate, or PET. It is used in composite materials with polyurethanes, collagen, 20-hydroxyethyl polymethacrylate, and gelatin in tendon replacement applications, cartilage, vascular grafts, abdominal wall prostheses, and replacement [53].

Polyurethanes

Polyurethanes are a class of polymers formed through the reaction of diisocyanates with polyols. They can be found in many products, including foams, coatings, adhesives, sealants, and elastomers.

Polyurethane foams are commonly used in furniture cushions, bedding, insulation, and packaging. They can be flexible or rigid and have a range of densities. Polyurethane coatings can protect against corrosion, abrasion, and chemicals and are often used in industrial settings. Polyurethane adhesives and sealants have strong bonding capabilities and are used in the construction industry for bonding and sealing applications [41, 54]. Polyurethane elastomers are used in various applications, including tires, rollers, and belts, due to their high durability and resistance to abrasion [55].

Polystyrenes

Polystyrenes (PS) are polymers with side benzene groups linked to the main polymer chain, and they are formed from addition reactions with an anionic catalyst [56]. This material has applications in tissue engineering and is currently the reference substrate for the growth, maintenance, and analysis of cell cultures. Like other polymers, it is important to perform a surface treatment to ensure good cell adhesion. In the case of PS, fibronectins, collagen, and gelatin can be used. It can also be treated with plasma, gamma rays, lasers, corona treatments, and strong acids [42, 56, 57].

Synthetic polypeptides

Synthetic polypeptides are developed by ring opening from α-amino acid N-carboxyanhydrides. Natural biological systems can produce self-assembled polypeptides and copolymers with specific sequences and compositions. Synthetically, homopolypeptides such as poly L-lysine, poly L-aspartic acid, and copolymers up to three blocks have been developed. These polypeptides can generate structures that mimic the extracellular matrix of cells, achieving very good biocompatibility and cell adhesion. However, the complex structures found in nature have not yet been achieved. The main applications of these proteins are as vehicles for controlled drug release systems, supports in tissue engineering, adhesives, antimicrobials, immunomodulants, and surface modification agents made of synthetic and natural polymers [58].

Polyolefins

Polyolefins are the structurally simplest polymers and are composed of aliphatic chains. Internationally, polypropylene (PP) and polyethylene (PE) are considered polyolefins. PP, for example, is used for sutures, while high molecular weight PE and its composite materials are widely used in orthopedic applications for total hip replacement, total knee replacement, and knee replacement in general. Bone [59].

Polyols

Polyvinyl alcohol (PVA) and its products are examples of polyols, i.e., polymers possessing hydroxyl groups in their structural makeup. Polyethylene oxide (PEO) and polypropylene oxide (PPO) are the products of oxidation [60]. Copolymerizing PPO and PEO with polyurethanes will produce chains with hard and soft segments, enhancing the durability of the final material. Heart pacemakers, infusion pumps, peritoneal dialysis, and other medical devices are among the applications of these copolymers. Vinyl acetate is used to create PVA, which is then converted into polyvinyl acetate (PVAc) and hydrolyzed to produce PVA [61]. PVA is a polymer that dissolves in water and may produce hydrogels by chemical or physical bonding [62-65]. PVA may also be used to create composite materials and mixes. Previous studies report mixtures of PVA/chitosan, PVA/cellulose, PVA/collagen, PVA/starch, PVA/hydroxyapatite, and PVA/PEO, among others [62]. Artificial corneas, contact lenses, an artificial pancreas, hemodialysis, controlled medication release systems, cartilage replacement, artificial tears, and supports for tissue engineering are just a few of the many uses for PVA. These applications are possible because of their hydrophilic properties and partial negative charge [62, 63, 66].

Thermosetting resins

The process of curing thermoplastic precursor resins yields thermosetting resins. As these resins are often liquids, crosslinking is used to convert them into hard solids [67]. Many chemical goods, including those for biomedical applications, are covered by epoxy and polyester resins. Epichlorohydrin and bisphenol A are the antecedents of epoxy resins, while dibasic organic acids and polyvalent alcohols are the precursors of polyester [63]. As these resins are often brittle, they are reinforced with materials like Kevlar, carbon (FC), and fiberglass (FV) [67]. Carbon fiber stands out in biomedical applications because it reduces allergic impact. These carbon fiber composite materials are often utilized in dental applications, bone plates, screws, external fixations (they specialize by providing equal strength and less weight than metal ones), and total hip replacement [9].

Natural polymeric biomaterials

Natural polymeric biomaterials are polymerized in living beings, whether animals, plants, microorganisms, or fungi, and subsequently isolated for use. This type of biomaterial and its derivatives have the advantages of high biocompatibility, good *in vivo* immune reactions, functionality, and durability [48]. These polymers can be classified into proteins, natural polyesters, and polysaccharides [64]. Carbohydrate-rich biomass-based sources include agricultural, paper, crops, green, and wood waste. Vegetable oils containing triglycerides include sunflower, meadowfoam, safflower, rapeseed, jojoba, castor, and soybean (fig. 4).

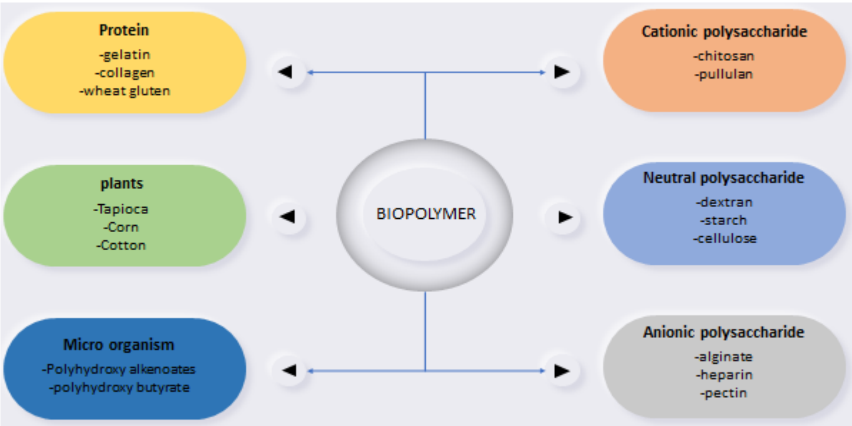

Fig. 4: Biopolymers according to their source (Source: author)

Proteins

Proteins are natural polymers made up of Lα-amino acids. In nature, there are around 20 amino acids, and their structure can be described in four levels: primary, which refers to the order of the amino acids present; secondary, which describes how the polypeptide chains fold into helices or sheets; tertiary, which describes how the secondary structures fold into a three-dimensional structure; and quaternary, which describes how multiple subunits of tertiary structures fold together [68]. In this classification, collagen, keratin, and fibroin stand out [65].

Collagen

Collagen, which makes up around 30% of animal protein, is thought to be the most abundant protein. Its vital importance is represented by the mechanical resistance of tissues and organs and physiological regulation [66]. The usage of collagen in the pharmaceutical sector has rapidly increased. It is now being utilized as a biomaterial for creating artificial skin, bone grafts, corneas, tendon implants, nerve regeneration, dressing systems, skin, and organs. These applications were made possible due to their strong cell adhesion and low toxicity [65, 66]. There are 21 distinct collagen types. Type I collagen is the most explored due to its excellent ability to produce fibers, thermal stability, and tensile strength. This biopolymer is created by separating it from various skin types, including those of pigs and cows [66, 69, 69].

Keratin

Keratin is a water-insoluble protein associated with intermediate fibers of epithelial cytoplasmids and epidermal appendages (hair, wool, claws, nails, etc.). It can be isolated to obtain films, fibers, sponges, hydrogels, and supports [67, 70]. Biomedical applications of keratin are still under investigation. However, *in vivo* and *in vitro* studies have shown that it induces cell proliferation, migration, and differentiation and promotes the regeneration of nervous tissue [67].

Fibroin

Fibroin is a fibrous silk protein composed of the union of glycine, alanine, and serine amino acids. Fibroin is biocompatible, biodegradable, permeable, has a minimal inflammatory reaction *in vivo*, and has high mechanical resistance. Fibroin has been used to manufacture matrices and cell cultures to form various tissues, including cartilage, since it facilitates cell adhesion and proliferation [63, 64, 71, 72]. It has also been used in sutures and wound dressings [65, 73].

Natural polyesters

Polyhydroxyalkanoates (PHAs), produced by bacterial fermentation of lipids or sugars as energy reserves, make up the majority of natural polyesters [68]. PHAs are formed as spheres in the body of the microorganism; due to their high production costs, they have had a niche market reduced to biomedical applications, where they are used for sutures, implants, heart valves or "stents" and supports for bone regeneration [74].

Polysaccharides

Simple sugars connect by glycosidic bonds are the backbone of polysaccharides. In biomedical applications, the major representatives are cellulose, starch, chitosan, alginate, and hyaluronate, with glucose as their basic structure [7].

Starch

Starch is composed of α-D-glucopyranose linked by bonds (1-4) and (1-6). This is a widely available, renewable, low-cost, and biodegradable polymer. The general procedure for the production of materials from starch involves its granular irruption through a combination of temperature, shear, and a plasticizing agent. The resulting material is known as thermoplastic starch (TPS) [75]. The biomedical uses of starch are the activation of supports in tissue engineering, drug-controlled release systems (tablets and pills), and microencapsulation of bioactive components [76].

Cellulose

Cellulose is the most abundant renewable biopolymer in nature. It is made up of D-glucose units linked by a β-1,4 glycosidic bond. This material is part of several living species (plants, animals, bacteria, and some fungi) [77]. Cellulose is a structural material in most species, characterized by its hydrophilicity, biodegradability, great capacity to be chemically modified, and high crystallinity [78]. Cellulose with dimensions below 100 nm is called nanocellulose. Bacterial nanocellulose (NCB) is an extracellular product of Gram-negative bacteria [79]. Among these is *Gluconacetobacter* sp., studied due to its efficiency in cellulose production and adaptability to different culture media [80]. Cosmetic products with bacterial nanocellulose can be found worldwide as an ingredient in moisturizing creams capable of penetrating the skin and carrying bioactive agents, rheology modifiers, and suspension stabilizers. Companies like L'Oreal and Procter and Gamble currently have products like Cellulon and NCB exfoliating face masks. Bionext, a Brazilian company, currently markets NCB as a temporary substitute for artificial skin [59, 81].

Chitosan

Chitosan is a natural polysaccharide derived from chitin. It is a copolymer of β-(1-4) glucosamine and N-acetyl glucosamine. The biocompatibility, biodegradability (mediated by lysozymes), non-toxicity and chemical similarity of chitosan with the components of the extracellular matrix of tissues such as chondroitin sulfate, keratan sulfate, and hyaluronic acid, render this biomaterial appropriate for use in tissue engineering, specifically, in the regeneration and repair of tissues such as skin, bone, cartilage, and nerves [82, 83]. Chitosan cytocompatibility and biodegradability have been observed *in vitro* with myocardial, epithelial cells, endothelial, hepatocytes, fibroblasts, chondrocytes, and keratinocytes [84].

Hyaluronic acid

Hyaluronic acid has important structural and biological functions in animal tissues. This polysaccharide is composed of subunits of β-(1-4)-D-glucuronic acid and β-(1-3)-N-acetyl-D-glucosamine. It has a great capacity for lubrication and water absorption, which influence several cell functions, such as migration, adhesion, and proliferation [85].

Alginate

Alginate is one of the biological molecules often utilized for mending and repairing human tissue, especially for wound dressing. This material may be found in seaweed. Since alginate is used to manufacture food intended for human consumption, it is thought to be safe for use in biomedical applications [86]. As a result of the cross-linking agents in the alginate dissolving and exchanging reactions with the monovalent cations present in the bodily fluids, alginate may also be considered biodegradable [87]. This is because alginate dissolves slowly in the body. The oxidation and reduction of the molecular weight of the alginate may each be used to determine the pace at which the alginate will dissolve [88]. In the end, the ability of alginate to form a gel is the primary factor that accounts for most of its applications, mostly in soft tissue engineering and wound healing. Nowadays, alginate is combined with other substances to produce composites made of alginate, which may be used for different sorts of biomedical applications [86].

Immune reactions of polymeric biomaterials

Although, by definition, biomaterials are designed to be biocompatible and can improve the quality of life of individuals, the complexity of biological systems makes this property difficult to achieve. Biocompatibility assays are evaluated under international standards (ISO or ASTM Standards) in cell models, hemocompatibility tests, toxicity, genotoxicity, mutagenicity, carcinogenicity, and animal models [89]. However, biomaterials could prompt immune reactions, even years after being implanted in the human body, which is a concern in research. The immune response is not trivial and includes a cascade of reactions of immune modulators [90, 91], such as interactions of biomaterials with blood, formation of a provisional matrix, acute and chronic inflammatory response, development of granulation tissue, foreign body reaction, and fibrosis.

Many of these immune responses are long-term or can be triggered suddenly [92, 91], rendering them not clearly understood. For example, polysiloxanes or silicones have been used in cosmetic surgeries since 1961, and despite their approval by the FDA, there is no complete knowledge of their interaction with the human body. Recent research indicates that the low-molecular-weight components of silicone implants can migrate into other tissues, triggering immune responses [93]. Within natural biomaterials, isolating collagen from exogenous (animal) sources is challenging [94, 95]. Reports by Keane *et al.* (2012) about the efficiency of the isolation of collagen demonstrated an association between the inflammatory response and the presence of exogenous proteins in the biomaterial [96]. Meanwhile, Requema *et al.* (2011) reported clinical cases of adverse reactions to injectable soft tissue implants made of biomaterials, such as collagen, PLA, hyaluronic acid, liquid silicone, PMMA, and polyamide and polyol hydrogels. The biomaterials generated edemas, granulomas, and inflammatory reactions in patients around the face and other body parts [97, 98].

Challenges and future prospects

Although, by definition, biomaterials are designed to be biocompatible and can improve the quality of life of individuals, the complexity of biological systems makes this property difficult to achieve. Biocompatibility assays are evaluated under international standards (ISO or ASTM Standards) in cell models, hemocompatibility tests, toxicity, genotoxicity, mutagenicity, carcinogenicity, animal models. However, biomaterials can present immune reactions, even years after being implanted in the human body, which is a concern in the research field. The immune response is not trivial and includes a cascade of reactions of immune modulators where the following are identified: interactions of biomaterials with blood, formation of a provisional matrix, acute and chronic inflammatory response, development of granulation tissue, foreign body reaction and fibrosis [95, 90]. Many of these immune responses are long-term or can be triggered suddenly, making them difficult for researchers to understand. For example, polysiloxanes or silicones have been used in cosmetic surgeries since 1961, and, although they were approved by the "Food and Drug Administration" (FDA), there is still no complete knowledge of their interaction with the human body. Recent research indicates that the low molecular weight components of silicone implants can migrate into other tissues, triggering immune responses [93]. Within natural biomaterials, the isolation of collagen from exogenous (animal) sources is a challenge for researchers. Reports by Keane *et al.* (2012) about the efficiency of the isolation of collagen demonstrated that there is an association between the inflammatory response and the presence of exogenous proteins in the biomaterial [94, 95]. Requema *et al.* (2011) present in their article, clinical cases of adverse reactions to injectable soft tissue implants made of biomaterials such as collagen, PLA, hyaluronic acid, liquid silicone and polyamide and polyol hydrogels [99]. The previous biomaterials generated edemas, granulomas and inflammatory reactions in patients around the face and other parts of the body.

Biopolymers have various uses in engineering, biology, and chemistry. They must be rigorously created to maximize the application of biopolymer goods. The medical applications of polymers depend on their biocompatibility, and modifications are necessary for them to be compatible with their applications. Bio-based polymers are being researched and developed to replace conventional polymers. Researchers are seeking alternative materials that may be created to replace petroleum-based polymers. Renewable raw materials are used to make bio-based polymers. The most recent advance in the plastics sector is intended to make plastics more biodegradable while preserving strength and durability comparable to typical plastics.

Nowadays, surgeons prefer materials made from natural resources because of their superior biocompatibility, lack of toxicity, and site-specific qualities. The need to heal surgical lesions or wounds, refill the damaged surface by activating cell proliferation, protect damaged tissues and wounds from bacterial contamination and inhibit infections, stop hemorrhagic bleeding, and reabsorb moisture from the wound has elevated the role of polymeric systems, which were previously used for simple sutures. Different antimicrobial agents have been utilized in conjunction with polymeric dressings. However, further research is needed into in vivo and ex-vivo models to determine the best approach. Therefore, maximizing the use of antibacterial agents in conjunction with polymeric dressings is crucial. New possibilities for managing chronic wounds may become available if novel polymeric formulations (filled with several antibacterial agents) are developed. Chronic wounds can be monitored and treated at the same time with the help of dressings that incorporate sensors and medicinal molecules. In a world where scientists can manipulate the characteristics of polymer systems by changing their temperature and pH or undergoing other external processes, sensitivity to external media seems to be gaining significance. Several multifunctional surgical materials may lie in the future of biopolymers due to the potential of altering them to give traits like sensitivity to external stimuli, gelling ability, and susceptibility to chemical alterations. However, many studies in this field have shown that current progress is limited and that these novel materials have enormous potential. This remains a challenge to progress in this field, so more in-depth study and innovation are needed.

CONCLUSION

Natural and synthetic polymers have considerably helped in biomedicine from ancient times. These polymers have been proven effective due to the versatility of their mechanical properties, biodegradability, and biocompatibility, validating their continued use in the future. The possibility of exploring copolymers, mixtures, composite materials, and surface modifications allows new developments in medical devices, tissue engineering, and regenerative medicine. However, the biocompatibility and immune response these polymers can generate is a constant concern, largely because these phenomena are not yet fully elucidated, rendering the biological interactions of human tissue with biomaterials unknown. As these mechanisms become known, we will be closer to developing high-performance biomaterials for improving the quality of life of individuals.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

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