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BİYOMEDİKAL UYGULAMALARDA KULLANILAN MİKROBİYAL BİYOPOLİMERLERE BAKIŞ

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Anahtar Kelimeler	Öz
Biyomedikal uygulamalar, Biyopolimer, Mikroorganizma.	*Mikrobiyal biyopolimerler, mikroorganizma, bitki vb. dahil canlı organizmaların ürünleri olarak tanımlanır. Biyolojik olarak parçalanabilir, biyouyumlu, toksik olmayan veya düşük toksik, anti enflamatuar ve antimikrobiyal aktivite gibi özelliklere sahip olabilirler. Polisakkarit, lipid ve protein olarak gruplandırılmışlardır. Mikrobiyal biyopolimerler, biyomedikal uygulamalar, doku mühendisliği, gıda endüstrisi, yara onarım sistemi, ilaç dağılımını içeren değişken sektörlerdeki biyomalzemeler olarak önemli bir kaynaktır. Bu nedenle, tıbbi implantların şeklinden dolayı bu alanlar için seçim kriterleri hayati önem taşımaktadır. Medikal uygulamalarda güvenli ve uzun süreli implant için bu kriterler pasif ve inert seçilmelidir.* *Bu derlemede, biyopolimer türevli mikroorganizmalar, özellikle aljinat, kitin, kitosan, levan, polihidroksalkanoatlar, hyaluronik asit ele alınmış ve mikrobiyal biyopolimerlerin biyomedikal araştırma alanındaki potansiyeline ışık tutmuştur. Biyomedikal uygulamalar için bu polimerlerin ekonomik faktörleri, biyosentezi ve özellikleri incelenmiştir. Mikrobiyal biyopolimerlerin olağanüstü derecede değişken olma ve uyarılmış özelliklere sahip olma yetenekleri, onları biyomedikal araştırmalardaki sorunları çözmek için avantajlı kılar. Mikrobiyal biyopolimerler, doku mühendisliği, tıbbi cihazların geliştirilmesi, ilaç dağılımı, kanser tedavisi ve yara iyileşmesi dahil olmak üzere bir dizi tıbbi uygulamada sürdürülebilir süreçleri düzenlemek için kullanılabilir. Bu nedenle bu biyopolimerlerin tarihçesi, özellikleri, ekstraksiyon yöntemleri ve uygulama alanları yaklaşımı üzerinde durulmuştur.*

INSIGHT TO THE MICROBIAL BIOPOLYMERS USED IN BIOMEDICAL APPLICATIONS

Keywords	Abstract
Biomedical application, Biopolymer, Microorganisms	*Microbial biopolymers are products of living organisms include microorganism, plant etc. They could be biodegradable, biocompatible, non or low toxic and show anti-inflammatory and antimicrobial activity. They have been grouped in polysaccharide, lipid and protein. Microbial biopolymers are important source as biomaterials in variable sectors consist of biomedical applications, tissue engineering, food industry, wound repair system, and also drug delivery. Therefore, the selection criteria are vital for these areas because these materials use for shaping of medical implants. These criteria should be elected passive and inert for safe and long-term implant in medical applications.* *In this review, biopolymers derivatives from microorganisms are handled especially alginate, chitin, chitosan, levan, polyhydroxalkanoates, hyaluronic acid and this review has highlighted the potential of microbial biopolymers in the field of biomedical research. For biomedical applications, the economic factors, biosynthesis, and characteristics of these polymers have been examined. The ability of microbial biopolymers to be extraordinarily variable and to have induced features makes them advantageous for*

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solving issues in biomedical research. Microbial biopolymers can be used to arrange sustainable processes in a range of medical applications, including tissue engineering, the development of medical devices, drug delivery, cancer therapy, and wound healing. Therefore, these biopolymers historical past, properties and extraction methods and application approach were emphasized.

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1. Introduction

The term of polymer is derived from the Latin words "polus" and "meros" which means "many part". The structure of the polymers consists of large, identical and/or comparable macromolecule chains with recurrent, long chains. The monomers that make up polymers are connected by covalent bonds, and macromolecules with high molecular weights are created in the process (Mohan et al., 2016). The primary themes utilized in the classification of polymers include polymer origin, chain structure, formation mechanism, temperature behavior, transport, crystallinity, and application area (Odian, 2004).

Commercial applications use synthetic polymers called "plastics" including PE (polyethylene), PP (polypropylene), PVC (polyvinylchloride), and PET (poly-ethylene terephthalate). Plasticizers, UV stabilizers, and other additives for synthetic polymers are generated from fossil basic sources such crude oil, coal, or natural gas (Othman, 2014). The most prevalent bio-based polymers in nature include polysaccharides (such as cellulose, etc.), poly-nucleotides (DNA, RNA), and polypeptides (Othman, 2014;(Chen et al., 2008; Othman, 2014)). Proteins (casein, whey, collagen), lipids (fatty acids, waxes, polyhydroxyalkanoates) and polysaccharides (alginate, pectin, starch, etc.), as well as cellulose, xanthan and other substances can all be converted into biopolymers. It can also be synthesized using materials originating from microorganisms (Çankaya and Sökmen, 2017).

Except the chemical synthesis, there are natural polymers being synthesized in living organisms and natural polymers has been known as biopolymers. The biopolymers are described as polymeric biomaterial which is formed by monomers. They are bonded each other to generate larger molecules (Mohan et al., 2016). The "bio" defines the source of materials as living organisms (Ghosh et al., 2021). Therefore "biopolymers" could be described as polymers that are synthesized by living organisms (Mohan et al., 2016). These biopolymers are synthesized by reactions catalyzed by enzyme (Jose et al., 2022) which bonds the blocks including amino acids, sugar, hydroxyl group and fatty acid to form the molecules possess high molecular weight (Moradalil and Rehm, 2020). Microorganisms produce these biopolymers at the very different classes (Gosh et al., 2021) and microbial polymers have the vital properties such as biodegradable, nontoxic, non-immunogenic, non-inflammatory and biocompatible (Jose et al., 2022). They are ideal for biotechnological use in biomedical application (Salernitano and Migliaresi, 2018) to compare especially synthetic polymers (Lee and Mooney, 2012). Although the synthetic polymers have been generally accepted, there is big problem about the accumulations of microplastics that causes the harmful effects in ecosystem (Jose et al., 2022). At the same time, using of non-biodegradable polymers in biomedical applications have some concerns about the surgical removal (Wani et al., 2016).

To decide on biomaterials selection is very important because it effect the shaped of medical implants. On the other hand, the criteria are to be chosen passive and inert for safe and long-term implant in medical areas. It is known real that any material could be evoked cellular response. That's mean, there are no material being totally "inert"; therefore, the most important feature of biomaterials to be considered is their interaction with the implanted tissue (Chesterman et al., 2020). Biodegradable polymers are usable in medical application as products for repairing or remodeling, but some properties are required for long-term materials stability:

1)To be feasible to manufacture consisting of available of bulk polymer in sufficient commercial quantities

2)The shown ability to shape polymers to be designed final product;

3)Mechanical properties that appeal enough short-term performance

4)To be low toxic of the products following degradation at local tissue reaction

5)Using as drug delivery system in extend release processes.

This review is organized as follows: In introduction is explained the description of polymers, classification of polymers, biopolymers, the criteria of biopolymer selection. Literature Survey is emphasized importance and the classification and properties of microbial polymers including alginate, chitin, chitosan, levan, hyaluronic acid and polyhydroxybutyrate. This is followed by definition, chemical and physical properties, application areas including biomedical, drug delivery, wound repair or wound dressing material, tissue engineering of these microbial polymers.

2. Literature Survey

2.1. Alginate

Alginate is defined as a group of edible anionic polysaccharides. Moreover, naturally it has been placed on the cell walls for brown algae such as *Macrocystis pyrifera*, *Laminaria hyperborea*, *Ascophyllum nodosum;* on the other hand this polymeris derived from various bacterial species (*Azotobacter, Pseudomonas*) and (Szekalska et al., 2016).

In the early 1940s, the irreversible hydrocolloid alginate material was developed. The search for an alternative for agar-based materials has been globally accelerated. When the main supplier of red seaweed was stopped exporting in Japan during World War II, brown seaweed native to the American coast was used as a new alternative. It has been observed that alginate from brown seaweed requires a minimum of simple equipment and instrumentation. In addition, it has been stated that it has superior properties than agar, with its speed of use, affordable price and user-friendly acceptance by patients. Since then, alginate has managed to become one of the most widely used materials in the world (Barr, 2020).

The extraction of alginate from seaweed is a multi-step process that usually starts with treating the dried raw material with diluted mineral acid. Alginate obtained after the purification steps is converted to the water-soluble sodium salt in the presence of calcium carbonate. It is then recycled back to the acid or expected salt (Szekalska et al., 2016). Figure 1 shows the procedure for the extraction of sodium alginate from brown algae.

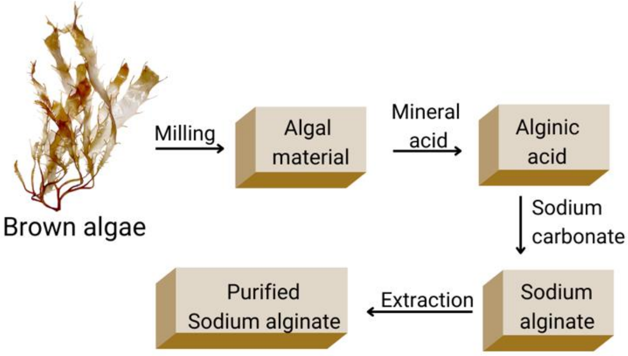

Figure 1. Extraction of sodium alginate from brown algae

When the alginate in algae cell walls is exposed to strong sea waves, it provides flexibility and a strong structure to the algae, protecting it from possible injury (Raus et al., 2021). The chemical structure of alginate, a linear biopolymer composed of 1,4-linked β-D mannuronic acid (M) and 1,4 α-L-guluronic acid (G) residues, is given in Figure 2 (Raus et al., 2021).

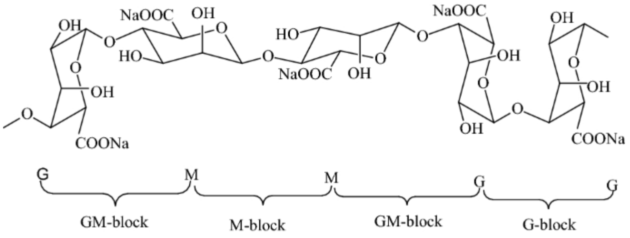

Figure 2: Chemical structure of alginate (Sahoo and Biswal, 2021)

A large amount of alginate biopolymer is encountered in nature due to the abundance of algae in water and living organisms all over the world. The annual production of industrial alginate is around 30,000 metric tons. It is estimated that less than 10% of the material is biosynthesized alginate. Therefore, there is adequate potential for developing alginate-based sustainable biomaterials (Pawar and Edgar, 2012).

Because of its properties such as biocompatibility, ease of gelation (Lee et al., 2012), low or non-toxicity, and non-immunogenicity, alginate has a wide range of applications in biomedical applications and engineering (Batista et al., 2019). Alginate hydrogels are used in wound healing, drug delivery and tissue engineering applications because they preserve the structural similarity in the cell. Wound healing alginate dressings provide a physiologically moist micro-environment. As a result, it promotes wound healing by minimizing bacterial infection in the wound area. Alginate gels can be used for cell transplantation in tissue engineering. Alginate gels are man-made tissue and organ replacements for patients who have lost an organ or tissue (Lee and Mooney, 2012).

A hydrogel film made of alginate and aloe vera was prepared for use in wound healing applications in a study reported by Pereira and colleagues (Pereira et al., 2013). The films were developed by combining the hemostatic properties of calcium alginate gels with the therapeutic properties of aloe vera. Depending on the type of wound, the resulting high-transparency gels can be applied to the wound in either dry or wet form. As a result, alginate/aloe vera hydrogel films have been demonstrated to have the potential to be used as a dressing for dry or wet wounds (Pereira et al., 2013). By the way, alginate biopolymer is widely used in the food industry as a food additive and component. Alginate is added to foods for the purpose of microbial and viral protection of fruits and vegetables. As a food additive, it is used as a gelling, thickening, stabilizing or emulsifying agent. Last but not least, alginate is preferred as a drug coating and drug delivery agent, such as the encapsulation of probiotics, thanks to its ability to encapsulate natural substances (Puscaselu et al., 2020). On the other hand, as well as the using of alginate often in biomedical applications, there are some disadvantages of this polymer. Mono-covalent cations dissolve alginate blocks in gel forms, whereas non-binding blocks are not degraded by bacteria found in mammalian hosts. Although alginate is a naturally derived polymer, some disadvantages of the application process should be known (Sahoo and Biswal, 2021).

2.2. Chitin

Chitin which is the second most common natural biopolymer after cellulose in the world, found in the shells of crustaceans such as shrimp, lobster and crab (el Knidri et al., 2018). At the beginning of the 19th century, chemist Henri Braconnot started working on chitin in France. In 1811, and defined chitin biopolymer as the insoluble residue left after extracting fungi with water, alcohol, and dilute alkali cork/mushroom. These residues were obtained from *Agaricus volvaceus, Agaricus acris, Agaricus cantarellus, Agaricus piperatus, Hydnum repandum, Hydnum hybridum* and *Boletus viscidus*. In 1823, Odier, described the insoluble substance he isolated from the exoskeleton of insects as chitin. (Crini and Lichtfouse, 2019; Batista et al., 2018).

The production of chitin biopolymer can be from three sources: crustaceans, insects and microorganisms. Commercial chitin is extracted from the shells of crustaceans such as shrimp, crab, lobster, and krill, which are supplied in large quantities by the shellfish processing industries. Chitin extraction is carried out by two methods, chemically and biologically. While acids and bases are used in the chemical method of chitin extraction, microorganisms are used in the biological method. Chitin can be extracted biologically using lactic acid bacteria. Further to that, mixed cultures of lactic acid bacteria and proteolytic microorganisms yield enough for extraction (Arbia et al., 2013)

The chitin biopolymer is a linear amino-polysaccharide composed of β-(1→4) linked 2-acetamido-2 deoxy-β-D-glucopyranose units and partially β-(1→4) linked 2-amino-2-deoxy-. The chemical structure of chitin is shown in Figure 3 (Ruiz and Corrales, 2017).

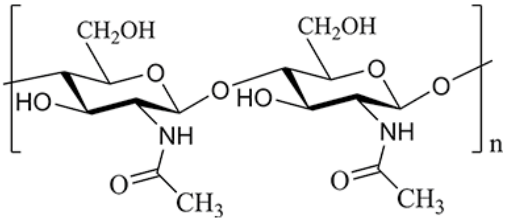

Figure 3. Chemical structure of chitin (Ruiz and Corrales, 2017)

Chitin and cellulose have structurally similar properties. Because of intramolecular and intermolecular hydrogen bonds, it is insoluble in water, aqueous solutions, and common organic solvents, just like cellulose. Chitin is a biopolymer closely related to proteins, minerals, lipids and pigments. As a result of the studies, it was stated that the specific properties of chitin, such as the degree of deacetylation and molecular mass, vary according to the process conditions (Arbia et al., 2013).

Chitin is a natural biopolymer that is non-toxic, biodegradable, and biocompatible. The chitin polymer is used in a variety of biomedical applications, including drug delivery, tissue engineering, and wound healing. Its benefits include the ability to easily process it into various forms such as membranes, sponges, gels, microparticles, nanoparticles, and nanofibers (Anitha et al., 2014). By the way, chitin is used in areas such as clarification of fruit juices and processing of milk including in the food industry. Except for food; It is preferred in many fields, including biosensors, due to its biodegradability, non-toxicity, physiological inertness, anti-bacterial properties, hydrophilicity, gel-forming properties and protein activity. Chitin-based biomaterials are used for the purification of industrial pollutants because chitin absorbs silver thiosulfate complexes and actinides. Another area of use is wound dressing and controlled drug release in medical and pharmaceutical applications. In dentistry, chitin is a hydroxyapatite-chitin-chitosan composite bone filling material that forms a self-curing paste for directed tissue regeneration in the treatment of periodontal bone defects (Rinaudo, 2006). In Figure 4, the processing possibilities of chitin biopolymer are given.

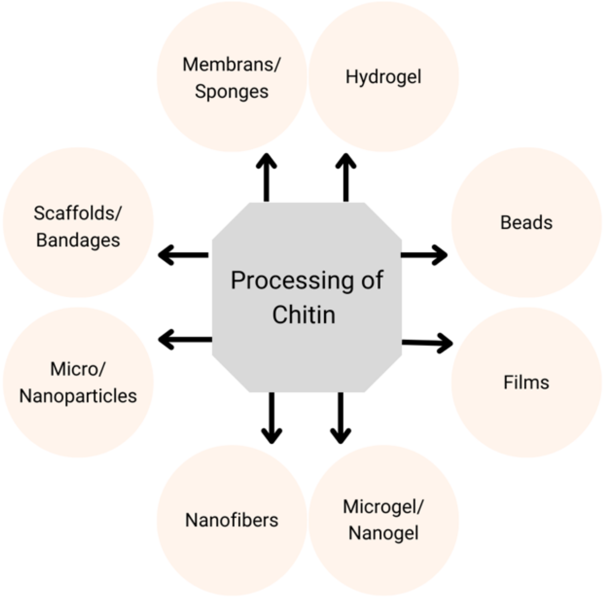

Figure 4. Processing possibilities of chitin biopolymer

2.3. Chitosan

Chitosan is a biopolymer formed when chitin becomes soluble in aqueous acidic medium when the degree of deacetylation reaches approximately 50% (Rinaudo, 2006). The chitosan biopolymer was first discovered by Rouget in 1859 by heating chitin in a concentrated potassium hydroxide solution. *Rouget observed that chitin became soluble with the applying of chemical and heat treatments. It was named as chitosan by Hoppe-Seyler in 1984* (Batista et al., 2018).

Chitosan is a biocompatible and degradable material derived from natural sources, such as the exoskeletons of insects, crustaceans, and fungi (Dash et al., 2011). In the microbial extraction of chitosan, microorganisms such as *Mucor rouxii* and *Phycomyces blakesleeanus* are used. Chitosan is produced using cell cultures of these microorganisms. The deacetylation of chitin occurs when *Aspergillus niger* is added to the culture medium. At the end of the incubation period of 96 hours, chitosan biopolymer is obtained (Kuzgun and İnanlı, 2013).

The chitosan molecule is a copolymer composed of N-acetyl-D-glucosamine and D-glucosamine units present in different degrees depending on the degree of acetylated moieties. The chemical structure of chitosan is shown in Figure 5 (Ruiz and Corrales, 2017).

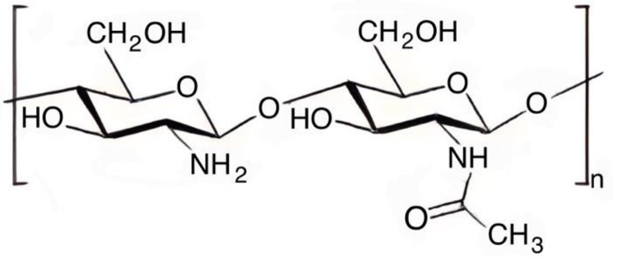

Figure 5. Chemical structure of chitosan (Ruiz and Corrales, 2017)

Chitosan is the only polycation in nature. The charge density varies according to the degree of acetylation and the pH of the environment. Chitin has a wide range of biological activities, including antitumoral, antimicrobial, antioxidant, and anti-inflammatory properties that make it suitable for use as a therapeutic polymer. Chitin has antimicrobial activity against a variety of microorganisms, including bacteria, filamentous fungi, and yeast (Aranaz et al., 2021).

The outstanding feature of chitosan over other biopolymers (cellulose, starch and galactomannans etc.) is that its chemical structure is suitable for specific modifications at the C-2 position without much difficulty. When designing polymers, special groups can be included next to chitosan for different applications (Rinaudo, 2006).

Chitosan, which has a different structure than synthetic polymers, is preferred in biomedical applications due to its physical and chemical properties, including the fact that it is biodegradable, non-toxic, and biologically compatible. Suspensions, solutions, particles, beads, resins, spheres, nanoparticles, sponges, gels/hydrogels, and membranes are all examples of applications for chitosan and its derivatives. This biopolymer is used in medicine, pharmacy, food industry, edible film technology, biotechnology, textile, and paper industries, in addition to practical applications. Chitosan is used in environmental applications such as water treatment, wastewater treatment, sludge dewatering, and membrane filtration because it is an environmentally friendly biopolymer (Anitha et al., 2014; Morin-Crini et al., 2019).

Chitosan is used as a polymeric mixture with chitin in tissue engineering through various modifications and combinations. These mixtures ensure the preservation of the porous structure of the scaffold in the tissue. It reduces the deterioration of the material and accelerates bone formation in vivo (Anitha et al., 2014). Chitosan films containing prednisolone are used in drug release. Layered polyelectrolyte capsules and chitosan gels are frequently used in the controlled release of drugs or proteins (Rinaudo, 2006). Food industry and nutrition are two other important applications for chitosan, which has indigestible high viscosity and high-water binding properties. As a dietary fibre, it reduces the absorption of fat and cholesterol and lowers cholesterol.

In the human body, chitosan and its derivatives promote weight loss and fat burning. Thus, it helps to lower systolic and diastolic blood pressure. Thanks to its prebiotic feature, it has the ability to improve the intestinal microbiota by increasing the bioavailability of probiotics. Chitosan has a wide range of applications in the beverage industry. The solution is used in the form of particles and beads. It is used in the clarification and filtration of fruit juices, wine, beer, tea, etc. products. Chitosan is preferred as a stabilizer, preservative, flavor enhancer and acidity regulator in various beverages (Morin-Crini et al., 2019).

2.4. Levan

Levan biopolymer is a biocompatible exopolysaccharide with potential uses in various industries. The origins of the levan biopolymer begin back to "natto," a traditional Japanese dish thought to aid in living a long and healthy life. Because levan is an important component of natton, it attracts the interest of researchers who prefer products supporting natural life (Öner et al., 2016). The beginning of studies on the production, collection and biosynthesis of levan was in Germany, France and England between 1870-1940. In 1930, the trade of polysaccharide polymers began in the United States (Srikanth et al., 2015).

Levan biopolymer is a β-(2,6)-linked fructose polymer obtained from different plant, fungal, yeast and bacterial sources (González-Garcinuño et al., 2018; Taran et al., 2017). Extraction occurs as exopolysaccharide from sucrose-based substrates by bacteria such as *Acetobacter, Bacillus, Erwinia, Gluconobacter, Halomonas, Microbacterium, Pseudomonas* and *Halomonas* species can be used as an alternative to many mesophilic levan-producing microorganisms. Halomonas species have industrial potential due to their production capacity that does not require sterile environment and high yield at high salt concentration (Tohme et al., 2018).

Levan is soluble in both water and oil due to its β-(2,6) bonds. While it is soluble in varying degrees in cold water, it is completely soluble in hot water. Levan biopolymer has no toxic properties. It also does not irritate the eyes. Levan stands out in the commercial industrial area, as it is a standard film-forming agent and a stable polymer (Srikanth et al., 2015).

The levan's film-forming ability, solubility in water and oil, strong adhesiveness, compatibility with salts and surfactants, low viscosity, heat stability, and acid-alkali stability allow it to be used in a variety of research and industrial applications. Levan is used in many biomedical applications such as stabilizer, emulsifier, thickener, encapsulating agent, osmoregulatory, food and feed additive, cryoprotectant, plasma substitute, drug activity extender, antitumor, antidiabetic and antihyperlipidemic agent in medicine. Levan synthesis, production and catalysis are becoming increasingly important due to potential applications in biomedical engineering (Çakmak et al., 2020; González-Garcinuño et al., 2018). The prominent features of levan in biomedical applications; biocompatibility, biodegradability, flexibility, edibility and being an environmentally friendly biopolymer. In addition, it has important biomedical properties such as antioxidant, anti-inflammatory, anti-carcinogenic, anti-AIDS, hyperglycemic inhibitor. Levan is a surfactant and natural adhesive (Srikanth et al., 2015). By the way, levan is also widely used in the food industry. Colloidal emulsions, aerosols and foams can be formed with Levan biopolymer. Levan can be added to food products as a beneficial prebiotic fibre for the gut microbiota. Yogurt, cereal products, fruit juices and bread can be given as examples of functional foods with adding of levan. It has also been stated that levan can be used as a fat substitute when phosphorylated (Haddar et al., 2021).

In a study has been reported by Gomes et al., 2018, it was determined that the membranes containing chitosan, sulfated levan and alginate developed have suitable conditions for different applications in the biomedical field such as biological adhesives (Gomes et al., 2018).

2.5. Polyhydroxyalkanoates

Polyhydroxyalkanoates (PHAs) can be synthesized by different types of microorganisms. The main production conditions are environments where essential nutrients (such as N, P, S, O or Mg) are limited and the carbon source is high. PHAs are used as a reducing agent or as a carbon/energy source. PHAs in polyester structure, which are similar to petrochemical plastics due to their physicochemical properties and are deposited in cell storage granules in microorganisms (Salehizadeh and van Loosdrecht, 2004).

PHAs produced by bacteria are of interest to researchers because they can be produced from renewable resources and are truly biodegradable and highly biocompatible thermoplastic materials (Chen and Wu, 2005). Depending on the requirements of different applications, PHA can be mixed with another polymer, enzymes or even inorganic materials such as hydroxylapatite to further adjust their mechanical properties or biocompatibility (Williams et al., 1999).

PHB materials physically show similar properties to petroleum-derived plastics such as commonly used polypropylene (Madison and Huisman, 1999). Showing thermo-plastic properties, PHB is four times harder than polyethylene. While PHB exists in the liquid phase inside the cells, it exists in the solid phase in the atmosphere. During extraction, PHB taken from the cells with the help of organic solvents tends to crystallize. PHB materials are hard and brittle, and their melting temperatures show the variation between 158 ˚C and 188 ˚C depending on their polymerization level. Because PHBs are thermo-plastic, they are resistant to pressure and can be shaped (Muhammadi et al., 2015).

The weights of PHB polymers can be between 60 and 2000 kDa (Braunegg et al., 1998). It is known that the localization of genes involved in PHB synthesis is on the chromosome or on plasmid DNA (Steinbüchel and Schlegel, 1991). PHB finds wide use in various industrial applications due to various reasons such as biodegradability, high biocompatibility and low toxicity (Chesterman et al., 2020). The molecular weights of the obtained PHB polymers are generally affected by various factors such as the type of bacteria used, the growth condition of the bacteria, and the place where the cells are in their life cycle (Dunlop and Robards, 1973; Taidi et al., 1994).

Many bacteria have the ability to store the energy and skeleton of carbon atoms as biodegradable compounds with polymeric structures and properties similar to synthetic plastics. However, these polymers can be produced or accumulated a few in industrially valuable quantities (Miu et al., 2022). Among the microorganisms that can produce PHA, are *Pseudomonas oleovorans* (Durner et al., 2000; Ramsay et al., 1991), *Pseudomonas aeruginosa* (Timm et al., 1990) and *Pseudomonas putida* (Tobin and O'Connor, 2005), *Ralstonia eutropha* (Durner et al., 2000), *Bacillus megaterium* (Gouda et al., 2001; Güngörmedi et al., 2014), *Bacillus drentensis* BP17 (Penkhrue et al., 2020), *Bacillus aryabhattai* (Balakrishna et al., 2020), *Geobacillus kaustophilus* (Gedikli et al., 2019).

Polyhydroxybutyrate (PHBs) are deposited after being produced as storage granules in the cell and structurally contain long polymer chains consisting of a combination of hydrophobic units containing short-chain β-hydroxy fatty acids. It is used as an intracellular storage material in prokaryotes (Poirier, 2002; Slater et al., 1992). It has been reported that PHB occupies a large volume inside the cell, and when looking at the right-hand helix structure, the presence of a double folded axis has been reported. The molecular structure of each strand contains twists that repeat every 0.596 nm (Anderson and Dawes, 1990).

PHB has used in tissue engineering scaffolds because of its ideal material properties. These properties are compatibility, support cell growth, guide and organize cells allow its applications in tissue growth (Wani et al., 2016). On the other hand, PHAs are particularly used in healthcare, which includes the manufacture of various medical materials such as suture threads, tissue repair devices, joint cartilage repair, nerve guides, and bone marrow skeletons (Koller et al., 2010). PHAs are also used in the manufacture of packaging for personal hygiene products, which are common in daily use, disposable table mats or bags that are biodegradable in nature. Although PHAs have all these advantages, they may find it difficult to find a place in the market because they are more costly than plastics produced by petrochemical means (Masaeli et al., 2013). Since PHA is biodegradable and biocompatible polymers, it can also be used in the synthesis of composites, which are widely used in wound healing, together with proteins that can be added to their structures (Quillaguamán et al., 2010). PHB and PHBV (β-hydroxybutyrate-β-hydroxyvalerate) can be given as examples of PHA derivatives polymers commonly used by researchers and biomedical industries (Williams et al., 1999). The brittleness of PHB is improved by copolymerization of -hydroxybutyrate with β-hydroxyvalerate (Chen and Wu, 2005). The variety of applications have been resourced from the elastomeric property of PHAs and its derivations. The PHAs have been applied in the multiple research areas because of its biological effective properties such as biocompabability, bioresorbability, biodegradability (Hinchliffe et al., 2021).

2.6. Hyaluronic Acid

Hyaluronic acid is a natural and linear biopolymer composed of disaccharide repeats, in which D-glucuronic acid (GlcUA) and N-acetylglucosamine (GlcNAc) are alternately joined by β-1,3 and β-1,4 glycosidic bonds. The chemical structure of hyaluronic acid is shown in Figure 6 (Liu et al., 2011).

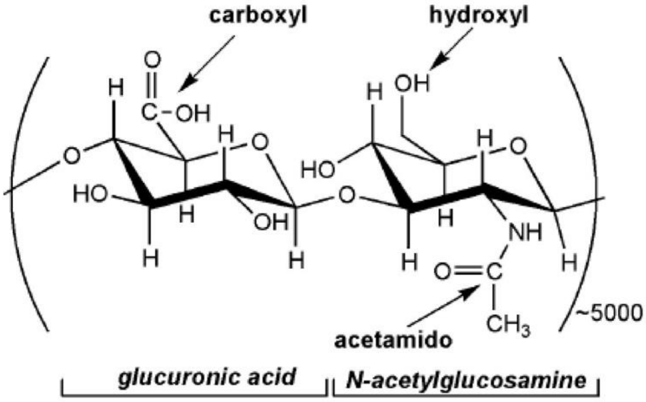

Figure 6. Chemical structure of Hyluronic Acid (Liu et al., 2011)

Hyaluronic acid was discovered for the first time in history by scientists named Karl Meyer and John Palmer. Meyer and Palmer described a new high molecular weight polysaccharide isolated from the vitreous of cattle eyes in their paper published in the Journal of Biological Chemistry in 1934. They named "hyaloid" (glassy glass-like appearance) for this new polysaccharide and hyaluronic acid derived from "uronic acid" (Selyanin et al., 2015). The term "hyaluronan" was added in 1986 to adapt to the polysaccharide terminology (Liu et al., 2011).

Hyaluronic acid can be extracted from various mammals and marine animals. Hyaluronic acid extraction was obtained from many sources such as vitreous body, umbilical cord, cock marrow and *streptococci* in the 1930s and 1940s. The yield and purity to be obtained vary according to the source and technique used. Industrial scale production of hyaluronic acid was first made by Shiseido in the 1980s. One of the most commonly used bacteria for hyaluronic acid production is *Streptococcus zooepidemicus* (Abdallah et al., 2020; Liu et al., 2011).

In one study, hyaluronic acid from *Streptococcus equi ssp.* was extracted with high efficiency. The bacterial production was performed at 33°C, on 24 hours and by shaking 187 rpm. As a result, hyaluronic acid with an average weight of 79416 Da was obtained with a simple and sequential method (Güngör et al., 2019).

In another study, hyaluronic acid extraction from fish eye and optimization of purification process were made. Hyaluronic acid was extracted and purified from the glassy humors of fish by following protein electrodeposition, detailed precipitation, selective recovery and membrane separation processes. With a waste material, low cost and high purity hyaluronic acid was obtained (Murado et al., 2012).

Hyaluronic acid belongs to the group of substances called mucopolysaccharides, which belong to the family of glycosaminoglycans (GAGs). Hyaluronic acid differs from other glycosaminoglycans groups because it does not contain a sulfate group. Hyaluronic acid has extremely slippery and hydrophilic properties (Saranraj and Naidu, 2013).

Hyaluronic acid is a one-of-a-kind biopolymer that can be assembled into extracellular pericellular matrices, has effects on cell signalling, and is viscoelastic and hydrodynamic. Thanks to these properties, it is preferred as a biomaterial (Falcone et al., 2006). Hyaluronic acid can be used in the human body because of important functions such as wound repair, cell migration and cell signalling. Because of its versatility, it is used in a wide range of biomedical applications, including tissue engineering and cancer treatment (Dovedytis et al., 2020). Biomedical applications of hyaluronic acid are shown in Figure 7. In tissue engineering, hyaluronic acid-based scaffolds are used. These scaffolds are biocompatible, degradable and absorbable. Polycations are added to improve the adhesive properties of hyaluronic acid-based scaffolds. Composite scaffolds formed in this way are very suitable for cartilage structures since they can synthesize advanced proteoglycans (Dovedytis et al., 2020). Furthermore, hyaluronic acid plays an important role in the biological processes necessary for wound healing and granular tissue formation, inflammation and generation of epithelium. It is also used in the treatment of external skin injuries, scars and chronic and acute wounds such as abrasions and burns. Thanks to the anti-ulceration feature of hyaluronic acid, stomach and duodenal ulcers can be treated (Yasin et al., 2022).

By the way, hyaluronic acid is used in cosmetic products to prevent and treat wrinkles, expression lines and fibroblastic depletion. Hyaluronic acid is a substance with a natural moisturizing effect. Unlike other humidifiers, it is not affected by relative humidity because it has good water retention at both high and low relative humidity (Yasin et al., 2022).

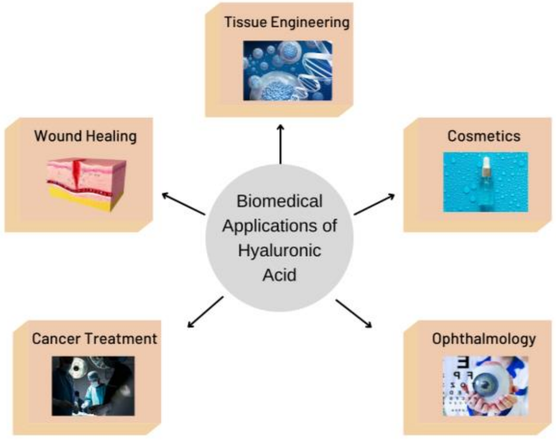

Figure 7. Biomedical applications of hyaluronic acid

3. Future Perspectives

Alginate, chitin, chitosan, HA, PHB, levan, obtained from renewable resources are only a few examples for biopolymers. The biological features of these polymers, which come from bacteria, algae, and fungi and can be used in a variety of industrial settings, have been compiled in Table 1.

Medical applications for biopolymers like chitosan and PLA silk are being researched more and more (Rebelo et al. 2017). The unique properties of biopolymers, like biocompatibility and biodegradability, provide significant benefits and increase the likelihood that they will be used in implantable medical applications. Since synthetic materials do not match the needs of biological systems, these novel materials are crucial in medicine. Recent studies have so shown that combining biopolymers with synthetic materials can transform medicine. The usage of non-renewable resources is raising environmental concerns, which is driving up demand for biodegradable polymers. Plastic packaging that is incorporated into society and supports a healthy, self-sustaining life is increasingly made of biodegradable polymers. It's even developing into the newest big thing. By 2023, the Markets and Markets annual report (Biopolymer's Market Forecast, 2020) projects that the market for biodegradable plastics would increase to $6.12 billion. In order to replace present polymers, bio-based polymers are currently undergoing study and development. Researchers are seeking for novel materials that can replace polymers generated from petroleum. Renewable raw ingredients make up bio-based polymers. These polymers now account for a negligible (less than 1%) share of the plastics market. By using a bacterial fermentation technique to create monomers from agricultural plants' renewable resources, bio-based polymers are created (Baranwal et al. 2022).

Table 1
Biopolymer's producers and properties

Biopolymer's Name	Producer Microorganisms	Effects/Properties
Alginate	*Macrocystis pyrifera, Laminaria hyperborea, Ascophyllum nodosum* (Szekalska et al., 2016)	Biocompatibility, ease of gelation, low or non-toxicity, non-immunogenicity (Lee et al., 2012)
Chitin	*Agaricus volvaceus, Agaricus acris, Agaricus cantarellus, Agaricus piperatus, Hydnum repandum, Hydnum hybridum, Boletus viscidus* (Crini and Lichtfouse, 2019; Batista et al., 2018).	Insoluble in water, non-toxic, biodegradable, biocompatible (Arbia et al., 2013; Anitha et al., 2014)
Chitosan	*Mucor rouxii, Phycomyces blakesleeanus, Aspergillus niger* (Kuzgun and İnanlı, 2013)	Antitumoral, antimicrobial, antioxidant, anti-inflammatory (Aranaz et al., 2021)
Levan	*Acetobacter, Bacillus, Erwinia, Gluconobacter, Halomonas, Microbacterium, Pseudomonas, Halomonas* (Tohme et al., 2018)	Film-forming ability, solubility in water and oil, adhesiveness, low viscosity, heat stability, acid-alkali stability, emulsifier, thickener, encapsulating agent, osmoregulator, food and feed additive, cryoprotector, plasma substitute, drug activity extender, (Çakmak et al., 2020; González-Garcinuño et al., 2018)
PHAs	*Pseudomonas oleovorans* (Durner et al., 2000; Ramsay et al., 1991), *Pseudomonas aeruginosa* (Timm et al., 1990) and *Pseudomonas putida* (Tobin and O'Connor, 2005), *Ralstonia eutropha* (Durner et al., 2000), *Bacillus megaterium* (Gouda et al., 2001; Güngörmedi et al., 2014), *Bacillus drentensis* BP17 (Penkhrue et al., 2020), *Bacillus aryabhattai* (Balakrishna et al., 2020), *Geobacillus kaustophilus* (Gedikli et al., 2019)	Biocompabability, bioresorbability, biodegradability, elastomeric (Hinchliffe et al., 2021)
HA	*Streptococcus zooepidemicus* (Abdallah et al., 2020; Liu et al., 2011), *Streptococcus equi ssp.* (Güngör et al., 2019)	Cell signalling, cell migration, viscoelastic, hydrodynamic, biocompatible, degradable, natural moisturizing (Falcone et al., 2006)

4. Conclusion

The potential of microbial biopolymers in biomedical research area has emphasized in this review. The economic aspects, biosynthesis and properties of these polymers have been addressed for biochemical applications. The microbial biopolymers have advantage for overcoming of problems in biomedical research, because these polymers can be varied extraordinary and have the induced properties. Sustainable processes can be organized with microbial biopolymers in variety medical applications consist of tissue engineering, medical device development, drug deliver, cancer therapy, wound repairment.

Author Contribution

In this review; Author1, Conceptualization, Investigation, Writing; Author2, Investigation, Writing; Author3, Supervision, review & editing.

Conflict Of Interests

The authors have not declared anu conflict of interests.

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