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Nature's prescription: decoding the power of biopolymers in medical and pharmaceutical applications

ABSTRACT

Over the past few years, the utilization of several biopolymers of natural, synthetic or microbial origin has witnessed a peak in various medical and pharmaceutical applications, like drug delivery, drug formulation, tissue engineering scaffolds, medical implants (e.g., prosthetics, stents), wound healing and dressing materials, and biosensing. This is mainly attributed to their ease of processing, biodegradability, high bioactivity, and biocompatibility compared to synthetic polymers. Moreover, a surge in the development of bio-/nanocomposites has emerged, with an aim to enhance the inherent properties of raw biopolymers derived from natural/microbial sources. This review is mainly focused on the different types of biopolymers or their composites utilized in medicinal or pharmaceutical industries and sheds light on the key advantages and limitations associated with their synthesis or use. Furthermore, the article presents a list of commercialized biopolymer composites with a discussion on the future scope of using these "gifts of nature" in medical field.

Keywords: *biopolymers; biosensing; drug delivery; surgical implants; tissue engineering*

1. INTRODUCTION

Petroleum-based synthetic plastics have become ingrained in everyday life by offering a convenient way to substitute for conventional materials in various applications. However, due to environmental concerns, this has fuelled a rapid move to phase out these synthetic plastics and embrace their natural counterparts [1]. Driven by the need for eco-friendly alternatives to synthetic polymers, there is burgeoning interest in the production of biopolymers from sustainable resources, like biowaste and biomass. Concurrent research efforts are also dedicated to the crafting of novel biocomposites and nanobiocomposites from natural fibres and biomass, offering high biodegradability and biocompatibility [2]. The remarkable ease of handling, reliability, and inherent chemical structure of these biopolymers or composites paves the way for their diverse applications across food, biomedical, and pharmaceutical industries [3]. Despite gaining commercial success in food and pharmaceutical sectors, biopolymers struggle with high cost and inefficiencies stemming from their synthesis, development, and post-processing steps [4]. The three main categories of natural polymers on the basis of their chemical structure include: (a) polysaccharides, (b) proteins, and (c) polyesters. Some protein-based polymers, including legumin, albumin, and gelatin, have garnered significant attention in medicine as nanodrug carriers, owing to their small size, increased stability, biodegradability, and non-toxicity [5]. Co-polymerization of specific polysaccharides (e.g., chitosan, cellulose, starch) with other polymers allows the engineering of biomaterials with tailored bioactivity, especially useful in biomedical applications [6].

Due to their excellent unique properties, natural biopolymers or their composites are weaving their magic in a plethora of medical applications, such as bone tissue engineering, targeted drug delivery systems, prosthetics, hydrogels, and drug formulations (Fig. 1). The use of a specific biopolymer for particular medical purpose is dictated by its fundamental characteristics, like molecular weight, mechanical properties, and degradation profile [5]. Biopolymers are mainly used in prosthetics and implantable devices with targeted molecule delivery, because of their non-toxicity, high selectivity, and biocompatibility [7]. Several biopolymer composites are used in surgeries across different medical fields, including cardiology and

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ophthalmology. Synthetic polymers can also be combined with other natural polymers for the designing of advanced skin scaffolds [8]. Biopolymers are extensively used in the fabrication of gels, films, and wound dressing materials that carry therapeutic agents for faster wound healing. For instance, chitosan is a biopolymer that can promote skin cell proliferation, making it a perfect choice for skin regeneration [9]. This review delves into the fascinating world of biopolymers or their composites for biomedical and pharmaceutical applications, with a special mention of the most commonly used biopolymers. The major research objective of this article is to discuss the various kinds of biopolymers or bio-/nanocomposites utilized across areas like tissue engineering and regeneration, surgical implants and devices, drug delivery, and biosensing. The review concludes with an understanding of the potential limitations, challenges, and intricacies in biopolymer design, alongside a glimpse into their exciting future perspectives in medicine.

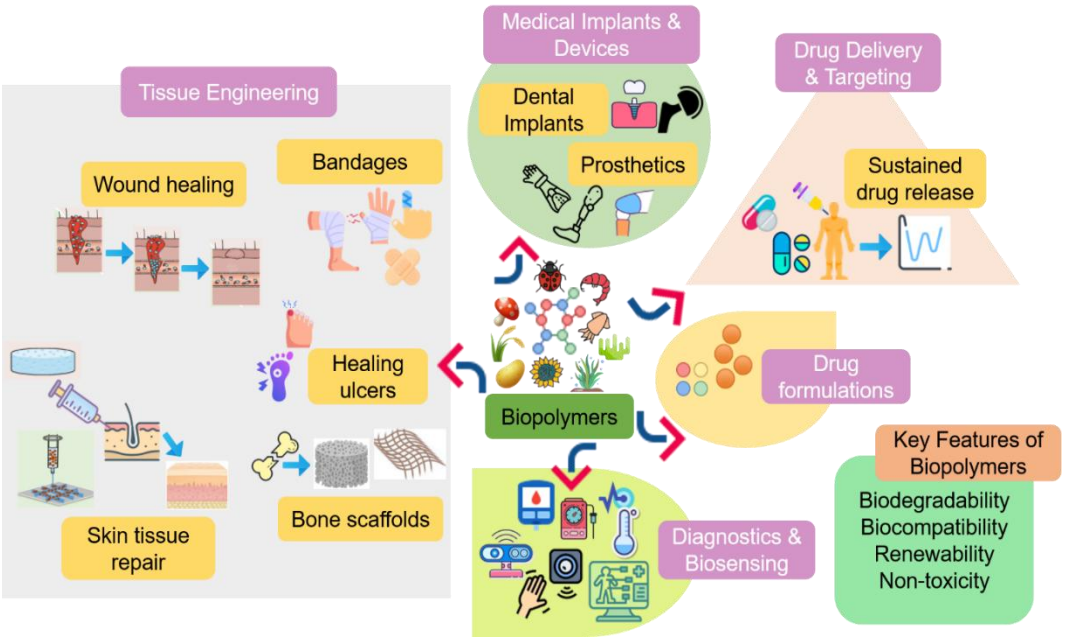

Figure 1. Applications of biopolymers in medicinal and pharmaceutical sectors

2. TYPES OF BIOPOLYMERS IN MEDICAL AND PHARMACEUTICAL APPLICATIONS

Biopolymers can be largely classified into two types: biodegradable or non-biodegradable, based on their nature of decomposition. Another major category of biopolymer grouping is based on their source of raw material, i.e., natural (e.g., plants and animals), synthetic (e.g., renewable sources and fossil fuels), and microbial (synthesized by microorganisms) biopolymers. Spanning from medical devices to environment-friendly packaging, these biopolymers possess functionalities suitable for applications across various sectors, including medicine, agriculture, agro-industries, sustainable packaging, and environmental remediation [10]. The different types of biopolymers utilized for medical and pharmaceutical purposes are explained below under separate headings.

Natural Biopolymers

Naturally derived biopolymers extracted from plant or animal biomass are either protein-based or derived from polysaccharides. Some of the well-known plant/animal-derived protein biopolymers include collagen, gelatin, elastin, keratin, fibrinogen, zein, soy protein, egg protein, milk protein, whey protein, and wheat gluten. Similarly, the carbohydrate-derived polymers come from diverse polysaccharide sources, such as agar, pectin, cellulose, galactan, carrageenan, chitosan, alginate, hyaluronic acid, gums, and starch. These biopolymers are well-suited for a wide range of medical applications, thanks to their biodegradability, biocompatibility, non-toxicity, and ability to bind bioactive molecules for healing and therapy [11]. Polysaccharides, composed of monosaccharide units connected via glycosidic linkages, are promising candidates for applications in tissue engineering and regenerative medicine [12]. Proteins, composed of amino acid chains, exhibit a diverse range of functionalities, such as motility, stabilization, elasticity, and scaffolding. Their ability to protect cells and tissues makes them ideal candidates for drug delivery and tissue engineering scaffolds [13].

Polysaccharide-based Biopolymers

Common polysaccharides used in medical applications include hyaluronic acid, chitin, chitosan, alginate, and starch. Hyaluronic acid is a non-sulfated, linear polysaccharide composed of glucuronic acid and N-acetylglucosamine units linked by *β*-1,4 and *β*-1,3 glycosidic bonds. It has a high molecular mass and unique polymeric and polyelectrolyte characteristics that contribute to its remarkable viscoelastic properties. High molecular weight hyaluronic acid also exhibits muco-adherent and anti-inflammatory properties. Hyaluronic acid, found in the extracellular matrix of cartilage, skin, and vitreous humor, has been used in a variety of medical applications [14]. The 1970s saw the first hyaluronic acid-based medical product approved by U.S. Food and Drug Administration, revolutionizing corneal transplants [15]. Chitin, a polysaccharide made up of 2-acetamido-2-deoxy-D-glucose residues linked by *β*-1,4 glycosidic bonds, is hydrophobic and insoluble in water and organic solvents. Chitin can be transformed into chitosan through deacetylation to increase its solubility in aqueous acids. Chitin and chitosan, characterized by their highly basic nature owing to the presence of high nitrogen content as compared to synthetic cellulose, are commercially attractive biomaterials for diverse applications. The multifaceted properties of chitosan, such as water sorptivity, biodegradability, oxygen permeability, hemostatic capacity, and ability to induce cytokine expression, qualify it as a versatile component for scaffolding materials [16]. Alginates are linear polysaccharides made up of copolymers from 1,4-glycosidically linked *β*-D-mannuronic acid (M-blocks) and *α*-L-guluronic acid (G-blocks) monomers. They are used for countless biomedical applications, such as cell transplantation and drug delivery, thanks to their biocompatibility, minimal side effects, and cost-friendliness. Starch is a polysaccharide distinguished into amylose and amylopectin, where the former is made up of glucose units joined by *α*-(1,4) bonds, and the latter is a branched molecule linked by both *α*-(1,4) and *α*-(1,6) glycosidic linkages. Starch-based biopolymers have carved a niche in diverse biomedical applications, like replacing and fixing bones, scaffolds for tissue engineering, and drug delivery [12].

Protein-based Biopolymers

Many protein-based biopolymers have shown immense potential in biomedicine sector. For instance, collagen's exceptional biocompatibility, biodegradability, low immune response, robust mechanical properties, and cross-linking ability, makes it perfect for tissue engineering and delivery of bioactive molecules. Cross-linking enables the fabrication of collagen into intricate 3D networks, serving as ideal scaffolds for tissue engineering [17]. The thermoreversible gelation behaviour of gelatin, combined with its excellent biodegradability and biocompatibility within physiological environments, renders it a preferred gelling agent for biomedical and pharmaceutical applications. Chemical cross-linking of either acidic or basic gelatin using glutaraldehyde or carbodiimide can improve the mechanical properties of gelatin scaffolds [18]. Silk protein can be processed into diverse formats, such as nanofibers, films, scaffolds, gels, and powders, making it ideal for applications like barrier membrane and drug delivery [19].

Synthetic Biopolymers

Chemically synthesized synthetic polymers can be obtained from biomass (poly lactic acid [PLA]) or are petroleum-based (e.g., polystyrene, polyethylene, polyamides, poly glutamic acid [PGA], polycaprolactone [PCL], and polyvinyl alcohol [PVA]) [20]. Lactic acid, the precursor in PLA synthesis, is made up of a carbon atom with two different configurations (L-/D-isomers). PLA is a hydrophobic semi-crystalline polymer with unique characteristics, like glass transition temperature = 40–70 °C, melting temperature = 130–180 °C, tensile strength = 44–59 MPa, and degradation time = 18–24 months. Owing to their outstanding biocompatibility and mechanical properties, PLA and its copolymers have been employed in a wide range of biomedical uses, including implants, sutures, stent matrices, tissue engineering, and drug delivery [21]. PGA is an exceptional anionic polypeptide made up of D- and/or L-glutamic acid units polymerized via *γ*-amide linkages between *α*-amino and *γ*-carboxylic acid groups. The fabrication of PGA scaffolds through gamma-irradiation or chemical cross-linking using hexamethylene diisocyanate or physical blending with poly (ethylene imine) is useful for achieving desirable scaffold properties [22].

Microbial Biopolymers

A diverse array of biopolymers produced from microbes include polyhydroxybutyrate (PHB), polyhydroxyalkanoates (PHA), and poly(3-hydroxybutyrate-co-3-hydroxyvalerate) (PHBV), gellan, dextran, curdlan, levan, and bacterial cellulose. Besides, a variety of microbial polysaccharides, including xanthan, exopolysaccharides, and capsular polysaccharides, are used for biopolymer synthesis. Precise genetic manipulation of microbes produces custom-made biopolymers perfect for cutting-edge medical applications, including drug delivery and tissue engineering. Moreover, medium and large-scale fermentation processes have paved the way for commercialization of many bacterial polymers [23]. PHAs, mainly synthesized by PHA synthase enzyme, can accumulate within

cells as insoluble spherical inclusions having a core composed of polyester and a surrounding protein-rich phospholipid layer. They possess a unique combination of desirable properties, e.g., biodegradability, biocompatibility, and thermoplasticity, crucial for medical devices and tissue engineering applications [24]. Lower crystallinity of PHB translates to its increased flexibility and ease of processing, making it ideally suitable for cell support matrix in tissue engineering [25]. Dextrans, characterized by their high density of accessible hydroxyl groups, cost-effectiveness, reduced immunogenicity, and clinical safety, are highly attractive materials for drug/protein delivery [26].

Biopolymer Composites

Biocomposites are a blend of biopolymer resin (outer layer) and natural fibres (as fillers), weaved together into mechanically strong and eco-friendly materials. A diverse range of methodologies have been adopted to shape these composites, like electrospinning, solvent casting, extrusion, phase separation, intercalation, laser printing, etc. [27]. Bionanocomposites synthesized using appropriate plasticizers and solvents exhibit improved thermal stability, mechanical strength, rigidity, and matrix elastic modulus. There are two categories of biocomposites: (a) matrix-reinforced fibres (e.g., PHA, cellulose, PVA) and (b) natural fibres (e.g., sisal, hemp, jute), on the basis of dominant material and its role in composite's properties [28]. Some naturally occurring biocomposites, classified according to the content of wood fibre as either wood or non-wood fibres, are abundantly rich in cellulose and lignin, thus exhibit high tensile strength and crystallinity. Biopolymer composites are superior over their counterparts (i.e., pure biopolymers) due to improved dimensional stability provided by hydroxyl groups in their chemical structure [29]. For example, polymers obtained from natural resources have attracted significant attention due to their biodegradable and environment-friendly properties. Moreover, surface modification of biocomposites allows fine-tuning of their unique properties, opening doors for their potential competition with conventional materials in various industries [30].

3. APPLICATIONS OF BIOPOLYMERS AND BIOPOLYMER COMPOSITES IN VARIOUS MEDICAL FIELDS

Tissue Engineering and Regenerative Medicine

Biocomposites are a valuable tool for supporting cell seeding, proliferation, and tissue formation, key steps in tissue engineering. Their effectiveness has been demonstrated in human skin fibroblast-based nerve regeneration models. Common biopolymers, including chitosan, collagen, and hyaluronic acid are vital tools in dermis and skin regeneration, cartilage repair, vascular engineering, and soft tissue repair. Biopolymer/ceramic composites exhibit remarkable flexibility, bioactivity, and mechanical strength, useful for scaffold construction in bone tissue engineering [22]. PLA, PCL, PGA, and PLGA are commonly employed biopolymers in building scaffolds for organs and tissues, which can mimic *in vitro* biological functions and promote cell growth and tissue regeneration [31]. Biopolymer nanocomposites are opening avenues for 3D-printing of organs, tissues, and body parts. This can create personalized scaffolds, mimicking intricate internal structures based on individual patient scans. Using this technology, nanomaterials such as nanotubes, nanofibers, and nano-structured particles can also be replicated [32]. Chitosan-based composites are used as bone graft substitutes in orthopaedic tissue engineering, owing to their strength, porosity, and osteoconductive properties. Moreover, excellent antibacterial and binding properties of chitosan composites render them as promising candidates for scaffolds in cartilage, bone, and disc tissue engineering [33]. Gelatin-chitosan-hyaluron scaffolds are effective in both soft and hard tissue regeneration, particularly in orthopaedics [8]. Chitosan incorporated single-walled carbon nanotubes are used for the fabrication of 3D films through laser printing [34]. Engineered polymer scaffolds made from materials such as hyaluronic acid, gelatin, collagen, elastin, and fibroin are used to regenerate a variety of tissues (adipose, ligament, blood vessels) and organs (liver, cartilage, bone, pancreas, spinal cord) [35].

A multitude of studies in the past have demonstrated the effectiveness of various biopolymers or their composites in tissue engineering. For instance, Pan et al. [36] created a hydrogel by combining oxidized dextran and modified gelatin for use in cartilage tissue engineering. The ability of this hydrogel to support cell viability was tested by using mesenchymal cells from the synovium, which have the potential to become chondrocytes. The hydrogel was loaded with mesenchymal cells and TGF-β3 (a growth factor) for use in an animal testing model. The results were impressive and the hydrogel not only supported cell growth, but also allowed for the differentiation of mesenchymal cells. A study by Dong et al. [37] explored the benefits of incorporating a chitosan hydrogel into a 3D-printed poly(ε-caprolactone) scaffold. The chitosan-containing scaffold promoted better cell retention, proliferation, and good mechanical strength in a rabbit testing model using bone mesenchymal cells and a growth factor. Silvestro et al. [38] investigated the ideal conditions for cross-linking chitosan with TPP (tripolyphosphate anion) and the effect of these conditions on resulting scaffolds' physical and chemical characteristics. Among the various concentrations (1 and 2%; *w/v* for chitosan and TPP) and cross-linking reaction times (2, 4,

and 8 h), the best formulation was identified to be 1% chitosan and 2% TPP due to high uniformity in the pore size (80 – 100 μm) of these scaffolds. Moreover, the scaffolds made with 1% chitosan, 2% TPP, and 8 h reaction time exhibited good cell viability. A hydrogel film was also prepared using chemically modified gelatin (gelatin-DTPH) and hyaluronic acid (HA-DTPH). The addition of HA-DTPH to this film offered two key advantages for effective tissue engineering process: (a) decrease in enzymatic degradation of gelatin-DTPH and (b) improvement in cell attachment to film surface [39]. Likewise, a hydrogel combining the properties of gelatin, hyaluronic acid, and hydroxyethyl acrylate was used in bone tissue engineering as an injectable material or a 3D-printed scaffold [40]. Gelatin nanofibers have also shown promise for tissue engineering retina and cornea in the eye. For example, a study by Xiang et al. [41] designed a biocompatible scaffold from gelatin, silk fibroin, and polycaprolactone that mimics Bruch's membrane (a layer that supports retinal pigment epithelial [RPE] cells to prevent blindness). The scaffold exhibited long-term growth of RPE cells and supported their functionalization. Incorporation of collagen or agarose into sodium alginate-based ink greatly improved its mechanical strength for 3D bioprinting in cartilage tissue engineering [42]. Salehi et al. [43] created a hydrogel combining alginate and chitosan and loaded it with olfactory ectomesenchymal cells for promoting nerve growth. *In vivo* testing of this hydrogel in a rat model confirmed better cell survival and function along with increased sciatic nerve regeneration abilities. Some commercially available biopolymer composites for tissue engineering and repair are listed in Table 1.

Table 1. Examples of biopolymer composites commercialized for tissue engineering processes

Product	Product information	Target tissue/organ	Purpose	Ref.
NeuroMatrix®	Type I collagen mesh Flexible tube	Nerve	Repair and regrowth	[44]
NeuroFlex®	Type I collagen mesh Flexible tube, kink-resistant	Nerve	Repair and regrowth	[44]
NeuroMend®	Type I collagen mesh Can wrap injured nerves for a range of injuries	Nerve	Repair and regrowth	[44]
Dynamatrix®	Acellular graft containing type I/II/VI collagen, glycosaminoglycans (hyaluronic acid, chondroitin sulfate A/B, heparin, heparin sulfate), proteoglycans, growth factors, and fibronectin	Skin	Wound healing, reconstruction of soft tissue	[45]
TachoSil®	Fibrin sealant (Human fibrinogen and thrombin on the surface of an equine collagen patch)	Heart	Sealant for cardiac wounds	[46]
Xelma	Blend of extracellular matrix proteins with propylene glycol and alginate	Skin	Healing of ulcer wounds	[47]
Dermagraft®	Cellular material (Human neonatal fibroblasts impregnated on bioabsorbable polyglactin mesh scaffold)	Skin	Healing of ulcers and other wounds	[48, 49]
Apligraf®	Cellular material (Foreskin-derived neonatal fibroblasts cultured *in vitro*, mixed with bovine type I collagen coated in cultured neonatal keratinocytes)	Skin	Healing of ulcers and other wounds	[50, 51]
BioDesign® Grafts	Water sealant (Acellular scaffold, non-cross-linked, non-dermis-based graft)	Brain, Abdomen, Heart, Skin	Brain surgery, abdominal reconstruction, wound healing, and heart surgery	[52]
INFUSE®	Absorbable collagen sponge in a metal Releases recombinant bone morphogenetic protein-2	Bone	Repair	[53]
DIABECELL®	Alginate-based porcine-derived islet of Langerhans cell product	Blood	Treatment of Type I Diabetes	[54]
NTCELL®	Alginate-based choroid plexus cell product	Brain	Treatment of Parkinson's disease	[54, 55]
HCE	Permeable polycarbonate substrate incorporated with immortalized human corneal epithelial cells	Eye	Repair of corneal epithelium	[56]

Drug Delivery and Targeting

Biopolymers make perfect drug carriers, thanks to their structural diversity, physiological compatibility, low toxicity, durability, renewability, and biodegradability (Fig. 2). Moreover, they are revolutionizing the pharmaceutical sector by aiding in drug formulation through protecting drugs and guiding their controlled delivery to the target. Different types of polysaccharides (structural, protective, and reserve) are primarily used in pharmaceutics because they can form conjugates with cell wall lipids and proteins. For example, biopolymers like cellulose, starch, gelatin, collagen, fibroin, and chitosan can be readily formulated into suspensions for the transport of variable size molecules. Supercritical fluid extraction, microemulsion, freeze drying, and electrospraying are some of the techniques used to deliver molecules at ocular, nasal, and dental systems [57]. The *in vivo* stability of biopolymeric nanoparticles was studied through their enzymatic degradation ability under different pH. Protein-based biopolymers were also explored for their potential applications via studying the relationship between their method of preparation and mechanism of drug release. These polymers with improved pharmacokinetic profiles ensured target-specific controlled drug delivery [58]. Temperature-responsive elastin-like polypeptides (ELPs) allow for precise and sustained drug release in intra-articular regions. ELPs possess self-clearance properties from the joint space, making them ideal partners for protein drugs and elucidating their effectiveness as "fusion proteins" at tumour sites [59]. Albumin microspheres were chemically modified with amino acid addition and cationization to target specific tissues. Efficient bioactive encapsulation and controlled drug release profiles can be achieved by employing certain techniques that harden these drug carriers [60]. Bacterial nanocellulose is an ideal drug delivery material that can carry albumin protein with its integrity and activity remaining intact. This paves the way for exciting applications of bacterial nanocellulose in target-oriented drug delivery systems due to their hydrophilic and biocompatible nature together with controlled release kinetics [61]. Natural biopolymers can be crafted into hydrogels or nanogels using methods like precipitation, self-assembly, spray drying, extrusion, and complexation. Dextrin is one such biopolymer that can be modified into hydrogels that are mechanically strong, highly stable, and facilitate controlled drug release. Further, nanogels prepared from dextrin find use in *in vivo* cancer treatment, thanks to their biocompatibility and low immunogenicity [62].

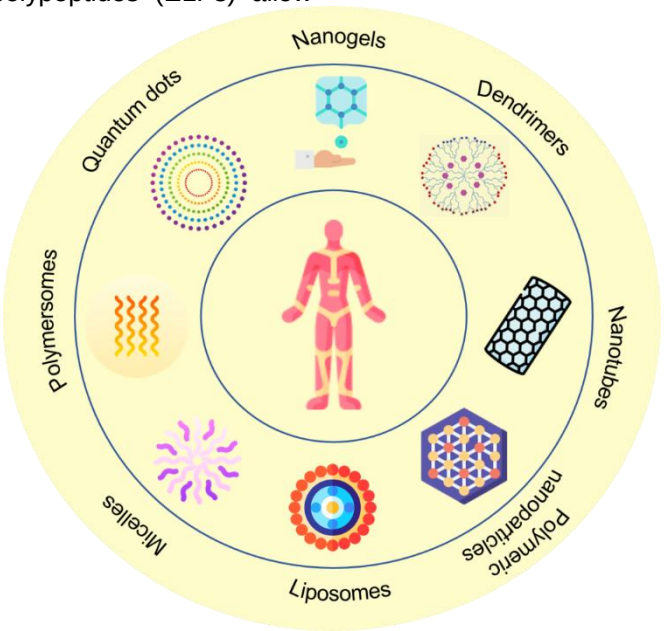

Figure 2. Types of biopolymeric drug carriers in drug delivery systems

Chitosan finds multifaceted applications in oral, nasal, ophthalmic, transdermal, and vaginal drug delivery systems. For example, in a study by Ren et al. [63], cinnamyl-chitosan was used as a potential material for formulating compressed tablets containing microcrystalline cellulose, magnesium stearate, and acetaminophen as binder, lubricant, and drug substance, respectively. Cinnamyl-chitosan offered several advantages owing to its larger particle size, excellent release of acetaminophen, improved mechanical strength, increased antibacterial and antioxidant activities, making it a popular excipient choice for manufacturing direct compression tablets. Hybrid microgels prepared using modified chitosan and silicon dioxide nanoparticles exhibited a smaller

hydrodynamic diameter and two-stage release profile for the entrapped vitamin B12, i.e., an initial burst release of high dose for rapid pain relief and slower, sustained release for the healing process over time. This is particularly useful for the treatment of gastric wounds using oral drug delivery systems [64]. Dexamethasone was topically delivered to the eye using self-assembled particles made from chitosan and cholesterol. These submicron particles with hydrodynamic diameters within 700 – 900 nm and zeta potential > 30 mV were non-toxic, had cell membrane protecting abilities, and long-term anti-inflammatory effects [65]. Chitosan-coated niosomes prepared using a modified thin-film hydration technique were able to improve the bioavailability of azithromycin for treating bacterial conjunctivitis. The niosomes facilitated sustained release of the drug at three times higher rate than the commercially available drops in rabbit's eyes [66]. In a study by Rosch et al. [67], chitosan-alginate nanoparticles were loaded with doxorubicin using a water-in-oil emulsification procedure. The particles were rapidly taken up by 4T1 murine breast cancer cells *in vitro*. In another work, Nalini et al. [68] investigated the effects of quercetin-loaded chitosan-alginate nanoparticles at varying pH, alginate-chitosan ratio, and quercetin concentration using ionic gelation method. The optimum conditions were identified to be: (i) 1:2 alginate-chitosan ratio, (ii) pH = 7.4, and (iii) quercetin concentration = 7.5 mg/mL, for the initial drug release (4%) for 1 h and sustained release (78%) over the next 24 h. A hydrogel incorporating an antifungal drug, i.e., clotrimazole, Eudragit® RS100 nanocapsules, pullulan, and polyacrylic acid (Pemulen® TR1) was created for treating vulvovaginal candidiasis. Slow and sustained release (20.14 μg/cm^2 in 8 h) of the drug along with its reduced penetration into the bloodstream (14 μg/cm^2) of cow vaginal tissue was achieved using this hydrogel [69]. Jackson et al. [70] developed cetyl trimethylammonium bromide (CTAB) surface-coated nanocrystalline cellulose for the delivery of anticancer drugs. The drugs, like paclitaxel, docetaxel, and etoposide could be delivered in a controlled manner for 2 days due to the effective uptake of these nanocrystals by KU-7 bladder cancer cells.

Surgical Implants and Devices

Several biopolymers, such as PLA and chitosan, naturally compatible and biodegradable, find diverse applications in pharmaceutical industries as implantable medical devices. Chitosan's versatility extends to various fields, like cardiology (e.g., heart valves), ophthalmology (e.g., contact lenses), and surgeries (e.g., regeneration of nerve) as medical implants [71]. Collagen serves as a supportive framework for bone, bone marrow and cardiovascular implants. PHAs can be used as implants in oesophagus, nerves, and vascular cartilage. Gelatin has profound applications across medical fields as bone replacements in surgeries, grafts in cardiology, and 3D skin models in dermatology. Chitosan composites are used to prepare bone scaffolds, bio-livers, and in bone and peripheral nerve regeneration. Likewise, hyaluronic acid implants can be used to build new vocal folds and cartilages in otolaryngology. PHBs can be fabricated to produce surgical implants and scaffolds for cell culture [8]. Biopolymers obtained from sources like proteins, polysaccharides, microbes, and their composites were synthesized using various techniques, including 3D bioprinting, freeze drying, casting, and electrospinning. They are versatile materials for manufacturing stents, barrier membranes, and as cargo to deliver medicines, cells, genes, or growth factors [22]. For example, a type I porcine collagen-based injectable medical device (Dental SKIN BioRegulation) was investigated for its effects on human gingival fibroblast cells. The cells grown on collagen exhibited higher viability and wound healing properties, promising the potential of this device as a suitable mechanical bio-scaffold [72]. A collagen bone void filler (CBVF) was also developed using collagen, chitosan, and modified single-walled carbon nanotubes. This injectable device exhibited improved mechanical strength and bioactivity [73]. Li et al. [74] evaluated the effectiveness of collagen scaffolds incorporating human umbilical cord-derived stem cells for the treatment of spontaneous brain bleeding. Patients receiving the scaffold had better think abilities, improved day-to-day activities, reduced spots of brain damage, and enhanced healing rate. A biodegradable urethral stent developed from gelatin and alginate exhibited good mechanical properties. When placed in the ureters of a female pig, the stent maintained normal urine flow, displayed no symptoms of inflammation, and remained intact for 3 days and degraded completely [75]. Likewise, an ab interno gelatin stent (XEN 45 gel stent) was developed as a glaucoma surgery device by Grover et al. [76]. The patients receiving the implanted device reported a decrease in intra-ocular pressure by ≥20% at 12 months with no signs of intraoperative complications. Hasan and Al-Ghaban [77] investigated the effectiveness of hyaluronic acid (0.1 mL gel) for bone healing around implants by measuring the levels of tumor necrosis factor (TNF-*α*). The increased expression of TNF-*α* around the implant indicated early post-surgical healing response as a result of enhanced bonding of bone with the hyaluronic acid. In another study, hyaluronic acid hydrogel prepared using microbeads (diameter = 140 μm and swelling rate = 800 –1200%) retained ~95% of its size even after 12 weeks of injection in rabbits. The hydrogel significantly subsided the inflammation after 8 weeks, leading to no fibrous capsule development or sub-chronic systemic toxicity in the rabbits [78].

Table 2. List of common biopolymers or their composites, showcasing their diverse applications, forms of use, and preparation technique in pharmaceutical industry

Biopolymer/ Biocomposite	Type of Biopolymer	Preparation Technique	Uses	Ref.
Biopolymers				
Albumin	Protein-based	Precipitation	Delivery of drug Ibuprofen	[91]
		Desolvation	Delivery of drug Irinotecan	[92]
Alginate	Polysaccharide-based	Dissolution	Delivery of drug Doxorubicin-loaded liposomes	[93]
		Precipitation	Delivery of drug Zidovudine	[94]
Bacterial cellulose	Microbial biopolymer	Gelation, cross-linking	Regeneration of muscle, vascular, and corneal tissues	[35]
Cellulose	Polysaccharide-based	Precipitation	Delivery of drug Betulinic acid	[95]
		Solvent evaporation	Delivery of drug Felodipine	[96]
Chitosan	Polysaccharide-based	Dissolution	Delivery of drug Quercetin	[97]
		Freeze-drying	Delivery of drug Curcumin	[98]
Collagen	Protein-based	Desolvation	Delivery of drug Fludarabine	[99]
		Electrospinning	Cardiovascular implants	[100]
		Freeze-drying	Delivery of drug Chloramphenicol	[101]
Elastin	Protein-based	Chemical synthesis/Acid solubilization/ Recombinant technology	Tissue scaffolds	[102]
Gelatin	Protein-based	Grafting, Electrospinning	Tissue scaffolds, Drug delivery	[103]
Hyaluronic acid	Polysaccharide-based	Chemical synthesis, cross-linking	Vocal fold implants, Tissue scaffolds	[35, 104]
Poly Lactic acid (PLA)	Synthetic biopolymer	Extrusion, Injection, Compression moulding	Drug delivery, tissue engineering, cell carriers, sutures	[105, 106]
Poly hydroxybutyrate (PHB)	Microbial biopolymer	Graft copolymeri-zation, Solvent casting	Nerve tissue engineering, Bone implants	[107, 108]
Starch	Polysaccharide-based	Dissolution	Delivery of drug Doxorubicin	[109]
		Prototyping	Tissue engineering (e.g., bone scaffolds)	[110]
Biopolymer composites				
Alginate/ agarose/ gelatin	Polysaccharide/ Protein-based	Gelation, cross-linking	Regeneration of cartilage tissue	[35]
Cellulose/ collagen	Polysaccharide/ Protein-based	Gelation, cross-linking	Regeneration of cartilage tissue	[35]
Chitosan-alginate scaffold	Polysaccharide-based	Coacervation	Regeneration of ligament and tendon tissues, Bone scaffolds	[111]
Chitosan/chitin/ gelatin composite	Polysaccharide/ Protein-based	Blending	Nerve grafts	[112]
Chitosan/collagen/ heparin scaffold	Polysaccharide/ Protein-based	Blending	Artificial liver	[113]
Gelatin/Polyethylene glycol (PEG)	Protein/ Synthetic polymer	3D printing	Administering cells to cutaneous wounds	[114]
PHB/PGA	Microbial/Synthetic biopolymer	Blending	Heart valve implant (in lambs)	[115]
Silk fibroin/gelatin	Protein-based	Moulding	Regeneration of ligament tissue	[35]

Diagnostics and Biosensing

A biosensor is an instrument used to translate biochemical information into electronic signals through an in-built transducer that can recognize the structures of different molecules. The device employs bioactive materials and turns molecular clues into precise quantifiable data, providing great opportunities in healthcare systems [79]. Biosensors have been used in wound dressing materials for monitoring a variety of parameters, like temperature, moisture, pH, and exudate release [80]. These built-in sensors can watch vital signs, such as moisture, pathogens, and necrotic tissues, guiding doctors to real-time intel for faster wound healing. This approach, especially crucial for stubborn wounds, including ulcers, diabetic foot, and bedsores, minimizes unnecessary bandage changes, provides barrier protection, and speeds up healing process [81]. Biopolymeric xerogels are cutting-edge tools in the realm of biosensing, relevant for studying important medical parameters (e.g., glucose level, cholesterol, uric acid, etc.). This is mainly attributed to their inherent properties, such as high porosity and surface area, making them perfect candidates for advanced biosensors [82]. Glycopolymer-based biosensors have been utilized for monitoring glucose levels, diagnosis of virus (e.g., influenza virus hemagglutinins), detection of antibodies in serum of diseased patients, neurotransmitter levels (e.g., dopamine), and measuring the protein concentration [83]. Cellulose acts as a robust and biocompatible substrate in anchoring the biological elements, like antibodies, enzymes, aptamers, etc. for optical biosensors. For example, a fibre-optic glucose biosensor was designed using glucose oxidase enzyme and carbon quantum dots impregnated within a cellulose acetate film. The biosensor was highly promising due to its high sensitivity, reusability, and ability to detect even low glucose levels [84]. Cellulose-based biosensors have also found exciting applications as diagnostic devices for elastase enzyme and used as a biomarker for various inflammatory diseases [85]. pH-sensitive hydrogels made from chitosan biopolymer have been used for treating asthma. Likewise, polyethylene glycol dimethacrylate-based hydrogel demonstrated *in vivo* efficacy against cancer by encapsulating the chemotherapy drug (doxorubicin) and gradually releasing it with response to change in pH around tumour sites [86]. Alharthi et al. [87] developed a specially designed nanocellulose acetate xerogel for the precise detection of urea. The gel contained two key components: (a) a urease enzyme (as catalyst) and (b) triarylmethane (for the determination of color change in presence of urea). Lee et al. [88] developed an amperometric biosensor using a xerogel-modified PtCr/C microelectrode for detecting carbon monoxide deposited on the surface of kidney. A glucose biosensor was also developed from a metal-organic framework (zeolitic imidazolate framework-8; ZIF-8) supported with cellulose acetate nanofibers and encapsulated with enzymes, i.e., glucose oxidase and lactose operon. The sensor was highly effective at detecting glucose and remained stable up to 15 h [89]. In another study by Ranjbar and Shahrokhian [90], an electro-chemical aptasensor was developed using a nano-composite made up of carbon/gold nanoparticles and cellulose nanofibers for the detection of *Staphylococcus aureus* infection in human serum. The sensor could detect the bacterial infection with a high detection limit of 1 CFU/mL. Table 2 provides an overview of the various applications of biopolymers or their composites in different forms within the pharmaceutical sector.

4. ADVANTAGES AND LIMITATIONS OF USING BIOPOLYMERS IN MEDICINE

Advantages

(i) Biopolymers are natural polymers that possess an array of advantages compared to synthetic polymers in terms of their cost-effectiveness, eco-friendliness, biocompatibility, non-toxicity, and safety [116].

(ii) The similarity of naturally occurring polymers with the macromolecules present in human body increases their biocompatibility with different body tissues/organs. Biopolymers, being non-toxic, do not lead to allergic reactions or severe inflammation, as their properties are identical to extracellular fluids [22,116].

(iii) Biodegradable biopolymers are highly suitable for drug delivery systems, as they do not require surgical removal after drug gets released to the target site and are excreted naturally from the body [11].

(iv) Biopolymer-based drug delivery system is highly suitable for systematic and standardized administration of drugs to a specified cell or tissue, prolonging their therapeutic response [117].

(v) Biopolymers allow sustained drug release, i.e., the drug is released slowly to the target site via degradation of polymer matrix in which the drug is embedded [118]. Biopolymers are highly desirable for this purpose, as they can be tailor-made into properties suited for medical applications, such as drug deciphering kinematics, degradation speed, and mechanical strength [119].

(vi) Biopolymers play a significant role in stimuli-responsive drug delivery matrices, which could be briefed as the ability of biopolymer-based drug delivery system to respond quickly to external factors (e.g., temperature, enzymes, and pH) and facilitate the delivery of drug at appropriate time and desired location [120].

(vii) Biopolymers are cutting-edge tools over their synthetic counterparts in the preparation of surgical materials, owing to their biocompatibility, safety, and unique characteristics at the target site [121].

(viii) Scientists and surgeons are capable of modifying and developing new materials with advanced structure and properties from pre-existing biopolymers by altering their response to external stimuli, gelling capacity, and vulnerability to chemical amendments. Therefore, architectural alteration of biopolymers can diversify the production of surgical materials, hence they seem to be the future of surgical industries [121].

(ix) Various biopolymers used in synthesis of biomedical materials due to their superior hygiene are given in Table 3.

Table 3. List of biopolymers utilized for the construction of biomedical materials (modified from [122])

Biomedical Materials	Applied Polymer	Probable Biopolymer
Surgical Sutures	Poly (amide), poly (propylene), poly (vinylidene fluoride)	PLA, PGA, PLGA
Wound dressing	Poly (vinyl alcohol), cotton	PGA, PLA
Tubing or blood or urine bags	Poly (vinyl chloride)	PBAT, PHB
Medical Catheters	High-density polyethylene (PE), Poly (dimethylsiloxane), polyether ether ketone, poly (propylene)	PLA, PGA, PLGA, TPS, PCL
Plasters	Toluene 3, 4 diisocyanate and polyethylene glycols (lycra fibers)	PLA, TPS
Surgical gowns	Cotton, polyesters, polypropylene (PP), PE	Bio-based (PET, PBT)
Caps, masks, and gowns	Polyethylene terephthalate, cotton	PLA, TPS
Surgical hosiery	PET, cotton, PP, PE	Bio-based PET
Pillow covers	Polyesters	PLA, TPS
Hospital Uniforms	Polyesters	Bio-based PET, TPS, PLA
Baby diapers	Polyacrylic acid, poly vinyl alcohol co-polymers	TPS

Abbreviations: PLA: Polylactic acid; PGA: Polyglycolic acid; PLGA: Poly (lactic-co-glycolic acid); PBAT: Polybutyrate adipate terephthalate; PHB: Polyhydroxybutyrate; TPS: Thermoplastic Starch; PCL: Polycaprolactone

Limitations

Although the unique properties of biopolymers have revolutionized the world of pharmaceutics and medicine, yet their expeditious usage is impeded by diverse factors.

(i) Of late, most of the research in this field has been carried out *in vitro*, which compromises its precision and actual outcomes practically. Hence, biopolymer products should be validated at pilot-scale level, before introducing them to actual world. Therefore, *in vivo* as well as clinical trials are required at large scale, in order to evidence the health advantages of biopolymers, particularly assessing their biocompatibility as an encapsulation material during drug delivery. Moreover, extensive studies are required to evaluate their disease treating capacity either alone or in combination for attaining suitable outcomes, when administered at highly specific and therapeutically admissible levels [123].

(ii) The other constraint being faced in using biopolymers for medical applications includes the problem of developing the material possessing properties superior or equivalent to artificial products by improving the inherent mechanical, thermal, barrier, kinetics, and release properties. This may overcome the issue of fast degradation, inferior mechanical solidity, and neutralizing the water absorption ability, especially during unfavourable conditions, interfering with the capacity of biopolymers in medical applications [124].

(iii) Another limitation in obtaining natural biopolymers from plants is linked with their production rate and chemical constituents, which depend upon the climate, season, place of origin, and species, which can affect water content of the biomaterial [125].

5. CONCLUSIONS

The quest for sustainable environmental solutions has turned its focus to developing "green" materials. With their environment-friendliness and impressive properties, biopolymers and their composites are being greatly valued as promising alternatives to synthetic polymers. Biopolymers are highly biodegradable, biocompatible, and non-toxic in nature. Their tailored properties find exciting applications in a variety of industries, especially biomedicine and pharmaceutics, where they are increasingly being used as implantable devices, tissue engineering scaffolds, wound dressing

materials, and drug delivery systems. The biopolymer market is booming due to increasing societal interest spurred by their sustainability appeal. However, high costs incurred with biopolymer synthesis hinder their widespread adoption, necessitating the need for developing affordable biomass substrates for large-scale production. Bridging the performance gap between biopolymers and their synthetic counterparts also presents a critical challenge. Upgrading the quality and performance of biopolymers via modification or combination with other components is an innovative strategy for overcoming these barriers and achieving a biopolymer commercialized future. To sum up, the positive impacts of biopolymers in different medical and pharmaceutical applications has sparked a lot of interest lately, raising the call for a complete phase out of synthetic polymers in future.

Future Prospects

(i) Biopolymeric drugs and gene delivery hold immense potential in shaping the future of medicine. They can be employed as targeted and customized carriers of drugs and genes to specific cell or tissue in living beings. This will aid in efficacious and prompt disease eradication with minimal side-effects.

(ii) Biopolymeric drug delivery systems require more focused research and efforts on gaining the stability and accessibility of drugs, especially for drugs with poor absorption rates and low solubility. This could add to promising and effective therapies of biopolymeric drugs in managing diseases.

(iii) Merging various smart technologies and materials with biopolymeric drug delivery systems can further revolutionize the world of medicine. In this context, nanotechnology, plasma technology, 3D printing, electrospinning, and cryogenic technologies could be a great asset in facilitating controlled release of drug and its absorption in the body. Hence, anticipated and explicit outcomes could be achieved (Fig. 3).

(iv) In order to upgrade the controlled and targeted aspects of biopolymer-based drug delivery systems, more precise and efficacious biopolymer processing techniques should be prioritized due to their indispensable role in vital processes.

(v) Synergistic therapies involving delivery of multitude drugs or genes concurrently targeting different parameters of disease or multiple medical conditions, is another important aspect of medicine that can be achieved through biopolymeric drugs.

(vi) In future, the biopolymeric drug delivery system can be upgraded by designing a high-tech system, which allows long-lasting and non-invasive drug delivery. Hence, recurrent administration of drugs can be overcome, improving the patient's docility and mental acceptance towards the treatment.

(vii) Rigorous research on the surface properties and functionalities of biopolymers is the need of the hour for breakthrough achievements in biomedical field, because surface and functional alterations can vigorously modify the material-cell interaction ability.

(viii) Further research should emphasize on developing hybrid biopolymers by combining different polymers and traversing their potential application in blended form.

(ix) Last but not the least, with advancement in biopolymeric drug delivery systems, authorities have to face the regulatory and commercialization issues. Hence, system has to prepare itself to address these challenges.

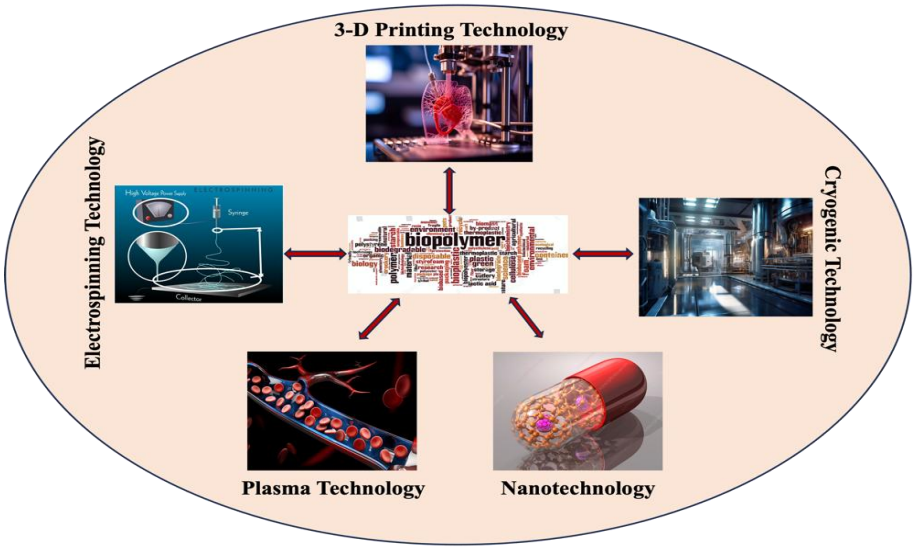

Figure 3. A diagrammatic representation of the networking of various smart technologies with biopolymers for effective drug delivery

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IZVOD

PREPIS PRIRODE: DEKODIRANJE MOĆI BIOPOLIMERA U MEDICINSKIM I FARMACEUTSKIM PRIMENAMA

Tokom proteklih nekoliko godina, upotreba nekoliko biopolimera prirodnog, sintetičkog ili mikrobnog porekla doživela je vrhunac u različitim medicinskim i farmaceutskim primenama, kao što su isporuka lekova , formulacija lekova, skele za inženjering tkiva , medicinski implantati (npr. protetika, stentovi), materijali za zarastanje rana i zavoje i biosenzivanje . Ovo se uglavnom pripisuje njihovoj lakoći obrade , biorazgradivosti, visokoj bioaktivnosti i biokompatibilnosti u poređenju sa sintetičkim polimerima. Štaviše, pojavio se porast u razvoju bio-/nanokompozita, sa ciljem da se poboljšaju inherentna svojstva sirovih biopolimera dobijenih iz prirodnih/mikrobnih izvora. Ovaj pregled je uglavnom fokusiran na različite tipove biopolimera ili njihovih kompozita koji se koriste u medicinskoj ili farmaceutskoj industriji i baca svetlo na ključne prednosti i ograničenja povezana sa njihovom sintezom ili upotrebom. Nadalje, u članku je predstavljena lista komercijalizovanih biopolimernih kompozita sa diskusijom o budućem obimu korišćenja ovih „darova prirode" u oblasti medicine.

Ključne reči: *biopolimeri; biosensing; isporuka lekova; hirurški implantati; inženjering tkiva*

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