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The role of biopolymers as therapeutic agents: A review

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ABSTRACT

In recent years, there has been a surge of interest in using biopolymer materials as natural possibilities for various biological applications. The current trend is a significant indication that it focuses on the theme of "green chemistry" or "green world," namely, a sustainable environment that is achieved by using materials and processes that are biocompatible, biodegradable, renewable, inexpensive, and efficient. The benefits of biopolymers in the biomedical field have been thoroughly demonstrated. Biopolymers (carbohydrates, proteins, polyesters, and polyphenols) and their biocomposites have attracted much attention in the biomedical sector (including wound healing, drug delivery, tissue engineering, and biosensors) due to their unique features. Biopolymers and their biological functions can be used to reduce the use of synthetic polymers. This brief review provides an update on recent research on the use of biopolymers and their types in the biomedical field, as demonstrated by several *in vitro* and *in vivo* experiments. Our efforts include a review of the practicality and biological potential of biopolymer materials as an important technique for more promising future therapeutic materials.

INTRODUCTION

Polymers are compounds formed from monomer units that are covalently bonded to make larger molecules. Their evolution began in the middle of the 20th century, when human existence was completely dependent on petroleum-based synthetic polymers in the industrial sector, which then led to the development of various types of innovations through engineering processes. The negative impact of the commercialization of petroleum-based materials, on the other hand, is not beneficial for the environment because it is not biodegradable. As a result, environmental awareness is growing rapidly, requiring the identification of renewable resources that can be used as an alternative to polymer manufacture that is safe for the environment and human health (Özçimen *et al*., 2017).

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Starting with this, there are several natural biomaterials with biodegradability features. Plants, animals, and bacteria may generate biopolymers, which are natural polymeric materials. However, the word biopolymer is still known by a variety of different names in the literature, including biopolymer, biobased polymer, bioplastic, and biodegradable polymer. Some publications suggest that biopolymers are biodegradable; however, they do not include biodegradable polymers that can be manufactured chemically. Biobased polymers are materials made from renewable resources, and these polymers may be biodegradable or nondegradable (Permatasari *et al*., 2022). Similarly, bioplastics may be biodegradable in certain cases since they are derived from biological sources. However, since they are not wholly generated from biological components, certain bioplastic-based polymers may also be classified as nonbiodegradable. The biodegradability of a polymer may be directly associated with its chemical structure, and its recency can be correlated with the origin of the monomer (Siracusa, 2019).

Biopolymers have several advantages over polymer materials derived from fossil fuels, including biodegradability, nontoxicity, and excellent biocompatibility. They can be used in various fields, including medicine (Park *et al*., 2021), pharmacology (Pantelić *et al*., 2020), food industry (Stoica *et al*., 2020), textiles, cosmetics (Abdellatif *et al*., 2021), agriculture (Lemboye *et al*., 2021), livestock sector (Yuan *et al*., 2019), waste-water treatment (Horue *et al*., 2021), bioplastics (Kabir *et al*., 2020), and biosensors (Sobhan *et al*., 2021).

Over the past few years, research on various themes of biopolymers has grown rapidly, with particular emphasis on their use in the biomedical field. Lee *et al*. (2020) released a scientific paper on the use of elastin-like biopolymer-conjugated C peptide hydrogels for long-term administration in patients with vascular dysfunction and diabetes. These data suggest that releasing peptide hydrogel biopolymer has the ability to reduce oxidative stress, inflammation, and endothelial apoptosis in hyperglycemia-induced diabetic rats. As a hydrogel, the biopolymer can provide benefits as a biomaterial for bone regeneration by stimulating mineralizing enzymes and antimicrobial agents (Panzella *et al*., 2017). Biopolymers with bioactive capabilities (also including antibacterial, cell proliferation, immunomodulatory, and angiogenic capabilities) provide a beneficial macroenvironment for regenerative physiological functions (Sahana *et al*., 2018). Given the dearth of research on the health-promoting qualities of biopolymers, this review focuses on providing more relevant information on the use of biopolymers, with a particular focus on their application to the promotion of human health.

TYPES OF BIOPOLYMERS

Biopolymers that are ecologically friendly are now being emphasized in many biomedical applications over the usage of synthetic biopolymer composites because they have excellent biocompatibility and biodegradability (Azeem *et al*., 2017; Torres *et al*., 2019; Wei *et al*., 2021). Polysaccharides (chitin/chitosan, starch, alginate, pectin, and konjac glucomannan), peptides (collagen, gelatin, and fibrin gel), biopolyesters, and polyphenols are examples of biopolymers. Various researches have extensively reported on the use of biopolymers in biomedical engineering, as seen in Figure 1.

Polysaccharides

Polysaccharides are natural and renewable polymers that provide an inexpensive and environmentally friendly source of raw materials (Thakur, 2018). Polysaccharides are often used as starting materials for the production of high-performance macromolecules such as starch, chitosan, chitin, cellulose, gums, and konjac glucomannan and their derivatives. From a medical point of view, polysaccharides can be considered as flexible macromolecules that can be used as drug delivery agents by enhancing drug delivery and as templates in developing specific therapeutic substances that can perform various tasks in the body. The functionalization of polysaccharide derivatives is also changed by adjusting their solubility, hydrophobicity, and physicochemical and biological properties (Ngwuluka, 2018).

Cellulose is a polysaccharide polymer of plant origin which is still combined in raw form with certain foreign components such as lignin, fatty resins, and minerals (Kalász *et al*., 2020). Cellulose consists of linear chains of glucose monomers linked together by glycosidic linkages (Mudgil, 2017). The production of cellulose derivatives and polymers has become an important step towards the use of biopolymers, which are considered a significant renewable resource in biomedical applications. For example, one of the ecologically beneficial approaches is the technology of processing lyocell from cellulose. Similarly, the development of engineering cellulose through the use of microorganisms to manufacture bulk polymers is highly anticipated for future technical advances (Aravamudhan *et al*., 2014).

Chitin is the most abundant polysaccharide in nature after cellulose and is derived from the cell walls of fungi, exoskeletons of arthropods such as crustaceans and insects, mollusks, and squid (Blanco *et al*., 2017). Chitin is a biopolymer formed from N-acetylglucosamine and glucosamine (Numata *et al*., 2011). Chitosan may be synthesized by chemically deacetylating chitin using % sodium hydroxide and heating it in a microwave. This heating may be applied in the last step of chitosan extraction, which is the conversion of chitin to chitosan (El Knidri *et al*., 2018). Deacetylation transforms 50% of chitosan into free amine with a heterogeneous chemical structure consisting of 1-4-linked 2-acetamido-2-deoxy—D-glucopyranose and 2-amino-2-deoxy—D-glucopyranose (Ibrahim *et al*., 2015). Because chitosan has great solubility in dilute organic acids, it may be utilized as a raw material for several scaffolds for biomedical purposes, contrasting chitin, which has reduced solubility in the aqueous phase or organic solvents (Nosrati *et al*., 2021b). Chitosan has been declared to have a health role and has been widely studied as a regenerative medicine (Jiang *et al*., 2021) included in the wound healing process (Mansouri *et al*., 2022), drug delivery (Kumari *et al*., 2021), implantation (Wohlfahrt *et al*., 2019), and functional food (Agarwal *et al*., 2021; Wang *et al*., 2021b). The introduction of chitosan as a vaccine vector is particularly impressive since it enhances the vaccine's potential to prevent infectious diseases such as viruses and bacteria by activating the immune response. Chitosan as a vaccine vector offers many benefits, including the ability to effectively load therapeutic medications, reduce drug toxicity and adverse effects, and increase vaccination efficiency (Meng *et al*., 2021).

Starch is formed by two glucose polymers, amylopectin and amylose. Amylopectin is a highly branched molecule consisting of several D-glucosyl units linked by 1,4- and -1,6-glycosidic bonds. Starch, for example, can come from carbohydrate-rich plants such as corn, cassava, rice, potatoes, and wheat. As a result, starch is widely used in the food sector. According to review studies, enzymatically produced starch has been found to be widely applicable in daily diets due to its antiglycemic activity (Himat *et al*., 2021). Starch is a suitable matrix for the release of phenolic chemicals that are regulated in the conservation of functional food components (Fonseca *et al*., 2021). A recent study demonstrated the function of porous starch in an enzymatically hydrolyzed corn starch film, which has a remarkable adsorption capacity for tea polyphenols. This finding is interesting because the gradual release of tea polyphenols with corn starch films exerts a significant protective effect when added to food (Miao *et al*., 2021). Konjac glucomannan (KGM) is a linear carbohydrate polymer comprised of 1,4-linked d-mannosyl and d-glucosyl residues, which is isolated from the tuber of *Amorphophallus konjac*. Because of its excellent water-binding and thickening capabilities, KGM has long been investigated as a possible biodegradable excipient in the food, pharmaceutical, and biomedical sectors (Abbasi *et al*., 2021). KGM has been employed in various studies as a potential drug delivery medium in a variety of disorders, either alone or in a biocomposite with other polymeric materials. KGM of various

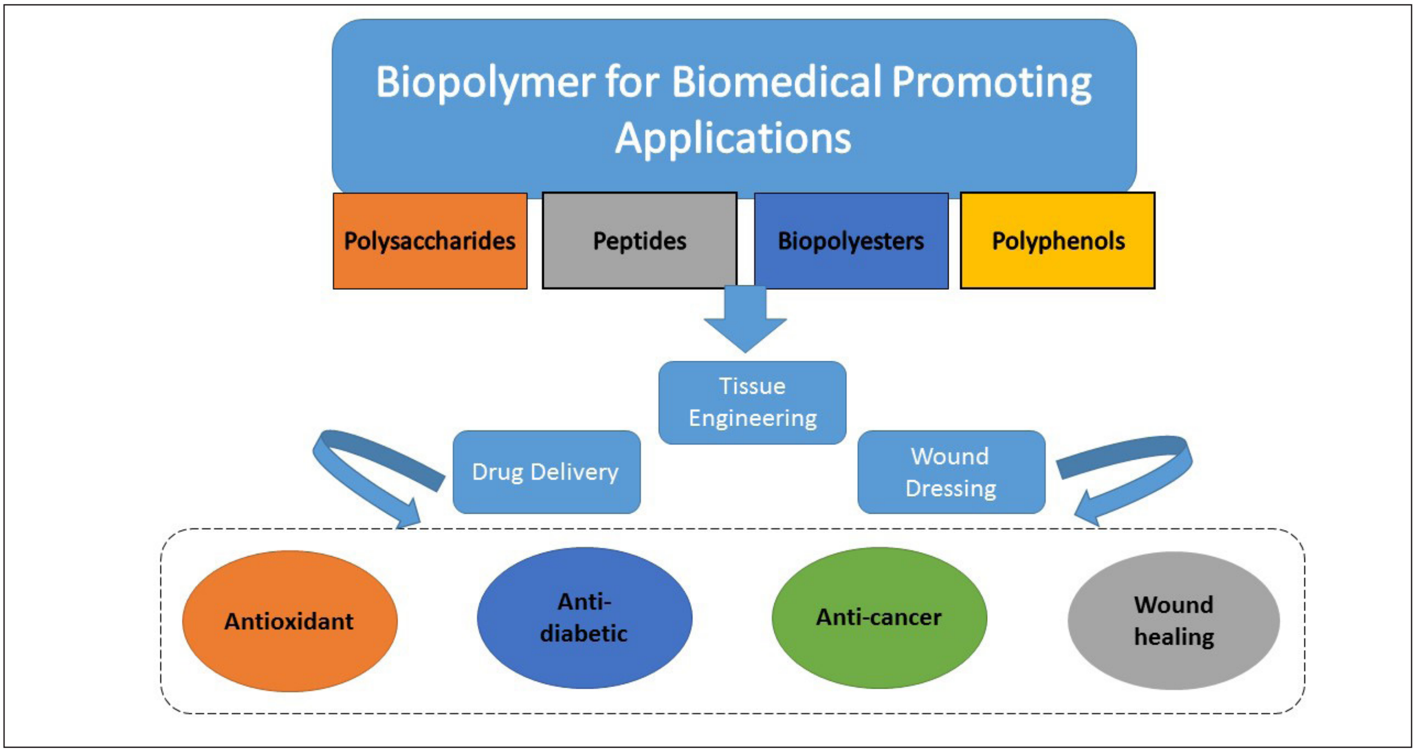

Figure 1. Schematic representation of the role of biopolymers applied in the biomedical field.

molecular weights was effectively described and administered to test animals, resulting in a rise in the levels of short-chain fatty acids (SCFA) in the colon (Yin *et al*., 2020). The capacity of KGM to lower oxidative stress levels is also emphasized via the nuclear erythroid 2-associated factor 2 pathway, as well as the nuclear factor-kappa B (NF-κB) route, which acts as a biomarker of anti-inflammatory and antioxidant activity in diabetic rats (Zhao *et al*., 2020).

Pectin is a biological polymer that contains galacturonic acid units and is commonly utilized in the food industry due to its ability to improve viscosity and bind water (Lipnizki, 2010). As a result, pectin, a form of structural fiber, is present in primary cell walls and intracellular layers of plant cells, particularly in fruits such as apples, oranges, and lemons (Mudgil, 2017). However, in recent years, there has been a surge of interest in the use of pectin as a health-promoting strategy, particularly in hypercholesterolemic patients (Marounek *et al*., 2010). Pectin, on the other hand, is said to be capable of preventing and treating intestinal infections, atherosclerosis, cancer, and obesity (Khotimchenko, 2020; Zhao *et al*., 2022). According to research, apple pectin molecule supplementation has an antiobesity impact on adult male Wistar rats caused by high-fed diets (HFD), as shown by enhanced activity of superoxide dismutase (SOD), glutathione (GSH) peroxidase, and catalase in the liver, kidneys, and blood serum (Samout *et al*., 2016).

Many algal polysaccharides are acquired from marine algae because they include a huge number of polysaccharides that are specific to the kind of seaweed, ranging from 4 to 75 % of the total dry weight (Usman *et al*., 2017). In recent years, there has been a sustained emphasis on the development of marine algal polymers in medicine, agriculture, and the food business so that they might have a positive influence on environmental quality (Azeem *et al*., 2017). This is possible because algae-based biopolymers have the potential to be exploited as environmental pollution remediation agents, adsorbents, and antioxidants (Kartik *et al*., 2021). Storage polysaccharides (starch and laminarian), structural polysaccharides (cellulose and alginate), and sulfate polysaccharides (agar, carrageenan, furcellaran, porphyran, ulvan, and fucoidans) are the three components of algal polysaccharides (Mišurcová *et al*., 2015). As a result of their biological activities, algal polysaccharides are receiving a lot of interest, particularly in the domains of health, pharmacy, and functional food production. Alginate microparticles are being developed in the biomedical and pharmaceutical areas due to their effective matrix capabilities for drug delivery agents, steady pH sensitivity to target medicinal components, and ability to reach up to the large intestine region for optimal absorption. This is critical since the degree of effectiveness of commercial inflammatory bowel medications necessitates multidrug administration over a lengthy period of time, which increases expenses and has adverse effects for patients (Agüero *et al*., 2017). The capacity of alginate-based scaffolding material to minimize vascularity and generate a minimal inflammatory response after transplantation was also confirmed. This demonstrates that alginate-based scaffolds may be used as a potential medication for tissue regeneration (Sun *et al*., 2013). Fucoidan, which is a sulfated polysaccharide obtained from marine algae, has been validated for its effectiveness by docking and *in vitro* against cervical cancer by blocking the action of histone deacetylase (HDAC) inhibitors receptors (Mustafa *et al*., 2021).

Microbial biopolymers such as exopolysaccharide (EPS) and polyhydroxyalkanoates are produced by various microbial taxa and are now being investigated as alternatives to contribute to more effective and environmentally friendly pollutant bioremediation

(Gupta *et al*., 2020). Due to their antioxidant and antibacterial properties, fungal EPSs are also widely used in biomedical applications. According to published reports, the EPS DHE6 produced by the fungus *Aspergillus* sp. significantly increased antioxidant activity, with a median effective concentration (EC_{50}) of 573.6 µg/ml, and strong antibacterial activity against *Staphylococcus aureus*, *Bacillus subtilis*, *Bordetella pertussis*, and *Pseudomonas aeruginosa* (El-Ghonemy, 2021). Interestingly, the EPS *Leuconostoc pseudomesenteroides* XG5 has the potential to act as a prebiotic by regulating the development of the mouse gut microbiota (Pan *et al*., 2020).

Peptides

Antihypertensive, antioxidant, antibacterial, and antiviral abilities are only a small part of the bioactive qualities of bioactive peptides, which are biomolecules produced from proteins and contain between 2 and 20 amino acid compositions (Cruz-Casas *et al*., 2021). Peptides found in animals, plants, and microbes have been the subject of much research and discovery (Pushpanathan *et al*., 2013). Due to the millions of bioactive molecules included in dietary protein, they are now recognized to have extra health benefits beyond their nutritional impact. Various diseases and risk factors can be treated using peptides derived from vegetable proteins. Plant-based peptides affect food and energy balance via hypothalamic signaling molecules, which may be potential targets for promoting a healthy diet (Kaneko, 2021).

Synthetic plant antimicrobial peptides are also emphasized for their potential use in food as natural preservatives that can help minimize food degradation, ingredient costs, and waste contamination (Rahardjo *et al*., 2022; Shwaiki *et al*., 2021). When added to the formulation, amaranth protein hydrolyzate, especially bromelain hydrolyzate-4 (B4), confirmed increased inhibition of angiotensin-converting enzyme-2 and dipeptidyl peptidase-IV (DPP-IV) (Kamal *et al*., 2021). The hydrogel material was prepared by combining oxidized dextran and modified hyaluronic acid with antimicrobial peptides in the presence of three bacterial pathogens (*E. coli, S. aureus*, and *P. aeruginosa*). Evidently, *in vivo* data show that hydrogels significantly enhance wound healing in diabetic rats by modulating proinflammatory markers [tumor necrosis factor-α (TNF-α), interleukin (IL)-1, and IL-6], increasing collagen deposition, and enhancing angiogenesis (Wei *et al*., 2021). The antimicrobial peptide is linked to a lytic peptide to the Michigan Cancer Foundation-7 (MCF-7) breast cancer cell-binding peptide and MDA-MB-231-mediated necrosis, a branched peptide synthesized into DNA oligonucleotides that promote apoptosis and caspase-3 activation (Sioud *et al*., 2012).

Biopolyesters

Biopolyesters are a major class of polymers made from biological monomers such as polylactic acid, polyhydroxy butyric acid, and polycaprolactone. Microbial polyesters such as polyhydroxyalkanoic and polyhydroxy acids have attracted interest due to their potential as sustainable alternatives to nonrenewable fossil fuel-based plastics/polymers. Moreover, they have been recognized for their potential for development in the pharmacology, biomedical, and agricultural sectors (Scaffaro *et al*., 2018).

Polyphenols

Polyphenols are natural substances that are present in a variety of foods and beverages. Polyphenols are abundant in fruits, vegetables, cereals, and beverages. According to reports, fruits such as grapes, apples, pears, cherries, and berries contain between 200 and 300 mg of polyphenols per 100 grams of fresh weight. Similarly, 100 mg of polyphenols is included in a glass of red wine and a cup of tea or coffee (Scalbert *et al*., 2005; Spencer *et al*., 2008). Polyphenols are also known as plant secondary metabolites and have important functions in plant defense mechanisms against pathogen aggregation (Kennedy, 2014). Interestingly, epidemiological studies and meta-analyses conducted towards the end of the 20th century showed that long-term consumption of polyphenol-rich foods might provide protection against the development of cancer, cardiovascular disease, diabetes, osteoporosis, and neurodegenerative diseases (Graf *et al*., 2005).

Flavonoids are the class of polyphenols that are most widely studied today. More than 4,000 variations of flavonoids have been found in various plant regions. Quercetin, myricetin, and catechins are just a few of the flavonoids found in nature. Flavonoids are also associated with the health industry because of their potential to treat various inflammatory disorders, including arthritis, gastritis, nephritis, hepatitis, ulcerative colitis, Alzheimer's disease, and atherosclerosis (Widhiantara and Jawi, 2021; Widhiantara *et al*., 2021). Flavonoids have antioxidant activity through regulation of the oxidative state and prevent damage caused by oxidative stress. Various cytokine indicators have been associated with chronic inflammatory disease, including TNF-α, IL-1, and IL-6. Importantly, several flavonoids, including luteolin, quercetin, and apigenin, have been shown to inhibit cytokine development and production. This may indicate the involvement of flavonoids as cytokine modulators. Flavonoids exert their pharmacological effects by inhibiting various enzymes, including cyclooxygenase (COX), aldose reductase, xanthenes oxidase, Ca^{2+} ATPase, phosphodiesterase, and lipoxygenase (Shukla *et al*., 2019).

Resveratrol (RV) is a nonflavonoid polyphenol molecule that is gaining attention for its many pharmacological benefits against various infections. These drugs have shown benefit in animal models of Alzheimer's disease and have few side effects. Resveratrol inhibits several elements of Alzheimer's pathogenesis by segregating A-peptides, decreasing levels of proinflammatory factors (NF-κB pathway), restoring Cyclic adenosine 3′,5′-monophosphate (cAMP) response element-binding protein levels, activating the silent information regulator 1 (Sirt1) signaling pathway, and regulating many autophagy pathways (Dhingra *et al*., 2021). Oral treatment of 10 mg/kg RV proved to be effective in reducing hepatic lipid formation, TNF-α, and malondialdehyde levels, as well as improving the antioxidant status of the liver (Bujanda *et al*., 2008).

Curcumin (diferuloylmethane) is a primary-secondary metabolite found in *Curcuma longa* and *Curcuma* spp. Curcumin is commonly used as a natural food coloring in Indonesia and has also shown a number of medicinal properties (Lestari *et al*., 2014). Curcumin has anticancer potential because it inhibits several intracellular signaling pathways in cancer cells. These signaling pathways include PI3K/Akt, JAK/STAT, mitogen-activated protein kinase (MAPK), Wnt/-catenin, p53, $NF_{K}B$, and apoptotic activity-related signaling pathways (Wang *et al*., 2021a). The anticancer effects of curcumin are also integrated into its molecular structure, in particular the presence of its diketone moiety in the keto-enol tautomer and tautomerism, which stimulates the interaction and binding of many enzymes. Lysyl oxidase, COX-2, xanthine oxidase, proteasome, Ca^{2+} ATPase, matrix metalloproteinase (MMP) inhibitor, histone acetyltransferase-1, HDAC, DNA methyltransferase 1, DNA polymerase, ribonuclease, protein kinase, protein reductase, GSH, isopropylmalate dehydrogenase, and peroxidases are some of these enzymes (Shehzad *et al*., 2014).

BIOMEDICAL APPLICATIONS OF BIOPOLYMERS

Polysaccharides and their biomedical effects

Polysaccharides are biopolymers formed from repeating residues linked by glycosidic bonds that can be extracted from plants, animals, and microorganisms. Polysaccharides are now used as application materials in the biomedical industry due to their stability and increased rate of synthesis. This is especially true for plant polysaccharides. Another explanation is that polysaccharides are very useful in the synthesis of pharmacological drugs delivery agents. This is due to the low biocompatibility, biodegradability, and immunogenicity of polysaccharides, which underlines its ability as a biopolymer material. The interaction of polysaccharides with biological tissues is also safe because of the various forms of polysaccharides, including functional groups such as carboxyl, amino, and hydroxyl groups. Natural polysaccharides, as previously indicated, have been investigated and emphasized internationally for a variety of positive reasons. Polysaccharides derived from various biological sources (plants, animals, and microorganisms) are currently among the most valuable hydrocolloids in the food and pharmaceutical industries (Behbahani *et al*., 2018). Here we summarize some of the findings related to the biomedical effects of polysaccharide biopolymers isolated from plants, animals, and microbes (Table 1).

In ethanol-induced mice, findings suggest that the plant *H. ulmarius* polysaccharide (HUP) has antioxidant, liver-protective, and lipid-lowering properties. Studies show that polysaccharides have importance in reducing hydrogen atoms or electrons in free radicals and that the main electronic donors may be hydroxyl and carboxyl groups, which are associated with antioxidant activity. Electron-withdrawing groups in polysaccharides, such as carboxyl and hydroxyl groups, result in a reduction in the O-H dissociation energy, resulting in the formation of a hydrogen atom. Low-molecular-weight polysaccharides, on the other hand, contain more reducing hydroxyl ends, which are used to react with free radicals, increasing antioxidant activity (Govindan *et al*., 2021). In the present study, one of the key mechanisms of HUP components in enhancing alcohol-induced liver protection is an increase in antioxidant activity.

Ocimum album seed polysaccharide fraction (OAP-1A) was studied and its antioxidant activity determined. X-ray diffraction analysis of OAP-1A confirmed that the polysaccharides in this material were amorphous or semicrystalline. The flexibility, density, viscosity, and functional characteristics of the biopolymer are other important variables, as is the ratio of the amorphous to crystalline area (Arab *et al*., 2021; Fu *et al*., 2019). The antioxidant ability of polysaccharides is generally determined by various parameters, including the presence of acid groups, phenolic compounds, protein impurities, and molecular weight (Keshani-Dokht *et al*., 2018; Nuerxiati *et al*., 2019). However, because OAP-1A excluded proteins and phenolic compounds in this study, the health benefits through free radical suppression are likely generated by hydrogen donation by the hydroxyl groups of polysaccharides (Arab *et al*., 2021).

Diabetes is a condition of impaired glucose and lipid metabolism (Anjana *et al*., 2020). Several previous studies have suggested the capacity of plant polysaccharide polymers to have a positive hypoglycemic effect in this approach (Chen *et al*., 2020). After research, the polysaccharide *Cynomorium songaricum* can lower blood glucose levels while increasing insulin levels, demonstrating its potential to reduce obesity and metabolic syndrome (Tao *et al*., 2019). The application of purple sweet potato polysaccharides induced in mice showed that it was able to stimulate the synthesis of short chain fatty acids (Tang *et al*., 2018).

Physiologically, increased insulin induces activation of the PI3K pathway, increases the intracellular Ca^{2+} content of islet cells, and increases insulin secretion, activation of the downstream protein kinase B (PKB or Akt) pathway, and stimulation of transcription and synthesis of insulin and glucokinase genes (Dumbrava *et al*., 2021). PI3K disorders can cause insulin resistance. On the other hand, the signal transducer and transcription activator (STAT-1) is involved in cell inhibition, signal transmission, and apoptosis induction. JAK-STAT is triggered by cytokines via receptor binding and subsequently promotes gene expression abnormalities in adipose tissue of diabetic mice. Polysaccharides from sweet corn cobs have been shown to influence the PI3K pathway through regulation of the Pik3r5 gene, which in turn affects insulin release and blood glucose levels, as well as the JAK-STAT signaling cascade (Wang *et al*., 2022).

Recently, various marine biopolymer compounds have been used to highlight cancer treatment developments. A recent study found that polysaccharides derived from five different varieties of bivalves were examined for their ability to inhibit human cancer cells (Padmanaban *et al*., 2022). The polysaccharide *D. variabilis* showed the greatest capacity to inhibit human cancer cells, with IC_{50} values in breast (MDA-MB-231) (350 µg/ml), cervical (HeLa) (350 µg/ml), liver (HepG2) (400 µg/ml), and colon (HT-29) (200 µg/ml) cancer cells. Proteins, carotenoids, pigments, terpenes, polyphenols, catechols, and polysaccharides are important constituents of other marine biota, such as algae. Terpenes, polysaccharides, and polyphenols, for example, are marine algae bioactive compounds that are opportunities for employees in the medical field today (Senthilkumar *et al*., 2013). Green algae, for example, include various polysaccharides (sulfate polysaccharides), brown algae (galactose sulfate, xylan, alginate, fucoidan, laminarin, and Sargassum agar), and red algae (carrageenan, xylan, and floridan) (Senthilkumar *et al*., 2013).

The most important target in cancer treatment is programmed cell death 1 (PD-1). In summary, the binding of PD-1 to programmed cell death ligand 1 (PD-L1), which is expressed on cancer cells, is a strategic approach to overcome detection by the host immune system. The low-molecular-weight brown algae polymer fucoidan (LMWF) is used to represent chemotherapy-targeted treatment in many investigations. Furthermore, LMWF polymers have been shown to suppress PD-L1 mRNA expression in HT1080 fibrosarcoma cells when combined with PD-L1 inhibitors in cancer therapy (Teruya *et al*., 2019).

Polysaccharide polymers were also investigated as drug delivery carriers to ensure maximum absorption by the body. Nanoparticles based on nanotechnology have emerged as promising carriers for various pharmaceutical agents, including protein and carbohydrate polymers. Polysaccharides have been in great demand as drug delivery materials because of their biocompatibility, biodegradability, low toxicity, and low cost (Torres *et al*., 2019). Encapsulation of the active ingredient with

Table 1. Summary of studies reporting the biomedical effects of polysaccharide polymers.

Source of biopolymer	Application	Main effect	References
Hypsizygus ulmarius (Bull.)	Antioxidant and hepatoprotective	Due to alcohol exposure, *H. ulmarius* promises antioxidant and hepatoprotective properties. The findings confirm that polysaccharides from *H. ulmarius* have the potential to be developed as a functional food that protects biological systems from oxidative stress caused by acute alcoholic liver disease	(Govindan *et al*., 2021)
Ocimum album	Antioxidant	The novel polysaccharide component of extracted *O. album* seeds was thermally stable and had significant antioxidant activity	(Arab *et al*., 2021)
Cynomorium songaricum Rupr.	Antidiabetic	A total of 35 potential antidiabetic biomarkers of *C. songaricum* were analyzed in serum, including 26 metabolites known to influence phospholipid metabolism, such as phosphatidylcholine, lysophosphatidylcholine, phosphatidylethanolamine, and sphingomyelin	(Shi *et al*., 2021)
Gloeostereum incarnatum	Anti-colon cancer	Polysaccharides from *G. incarnatum* inhibit tumor development by suppressing levels of IL-1, IL-4, IL-6, IL-17, IL-22, TNF-α, and MMP-2 and increased levels of IL-15 and IL-18	(He *et al*., 2021)
Polygonatum sibiricum	Bone regeneration	Polysaccharides from *P. sibiricum* showed proliferative activity and increased osteogenic viability of bone marrow mesenchymal stem cells (BMSCs) in mice, suggesting that they can be administered as osteoporosis therapy	(Zong *et al*., 2015)
Marine bivalves	Anticancer	*Donax variabilis* polysaccharide inhibitory effect on the breast (MDA-MB-231), cervical (HeLa), liver (HepG2), and colon (HT-29) cancer cells	(Padmanaban *et al*., 2022)
Quercetin encapsulation with soluble soybean polysaccharide (SSPS) and chitosan	Anticancer, anti-inflammatory, and antioxidant	When compared with nonencapsulated quercetin, its biological activity was mostly through the encapsulation phase of SSPS material with chitosan. This shows that SSPS and chitosan nanoparticles will be more useful in drug and food applications	(Moon *et al*., 2021)
Flammulina velutipes polysaccharides (FVP)	Intestinal health promotion	For 28 days of treatment, FVP supplementation was able to induce better gut microbiota, villous morphology, and gut physiological metabolism in rats	(Hao *et al*., 2021)
Microbial polysaccharide	Tissue engineering	Cell proliferative activity in in vitro and in vivo investigations was demonstrated by microbial polysaccharide hydrogels developed for biomedical purposes. Polysaccharide hydrogels have the potential to be used as cell devices in tissue engineering	(Qi *et al*., 2020)
KGM	Antidiabetic	Through regulation of the Nrf2 and NF-$_k$B pathways, fiber-rich KGM was able to reduce oxidative stress and anti-inflammatory effects in diabetic rats	(Zhao *et al*., 2020)
Silver nanoparticles (AgNP s) composited in konjac glucomannan + chitosan	Wound healing	AgNPs bioassembled with KGM hydrogel and chitosan modulated silver ion release in mice, reducing wound and inflammatory responses	(Jiang *et al*., 2020)
Konjac glucomannan microparticles	Antitubercular drugs	Spray-dried konjac glucomannan microparticles with additional advantages for inhalation exposure to antituberculosis drug administration	(Guerreiro *et al*., 2021)

soy soluble polysaccharide (SSPS) nanoparticles and chitosan has many biomedical applications, as evidenced by their antioxidant and anti-inflammatory activities when dissolved in media and delivered to macrophage cells. Interestingly, western blot findings showed that quercetin-encapsulated nanoparticles were more efficient than unencapsulated free quercetin crystals in lowering iNOS levels, confirming their effectiveness as antioxidants and anti-inflammatories (Moon *et al*., 2021). Furthermore, AgNPs composited in KGM hydrogel and chitosan were shown to be efficient in accelerating wound healing and reducing inflammation in mice (Jiang *et al*., 2020).

Peptides polymers and their biomedical effects

Peptide polymers produce competitive stability, cheap cost, simplicity of modification, large-scale manufacturing, and different activities, which act as references to guide their application as nanomedicine polymers for improved drug delivery (Komin *et al*., 2017). Several *in vitro* and *in vivo* research models are being used to investigate the application of peptide polymers in the biomedical sector (Table 2).

The development of implantable biomaterials and medical devices such as catheters, pacemakers, and contact lenses has benefited contemporary healthcare systems over the past few decades. As a result, long-term research into efficient antibacterial agents used to preserve thermoplastic polyurethane (TPU) surfaces is of great importance in the use of biomedical materials. An innovative invention describes the polymerization of N-carboxyanhydride stimulated by lithium hexamethyldisilazide for the manufacture of peptide polymers. TPU surfaces modified with host defense peptides simulated polymers exhibit strong antibacterial properties against Gram-positive and Gram-negative microorganisms. These findings validate the strong biocompatibility, low cytotoxicity, and good histocompatibility used to protect implanted biomedical devices and tissue-engineered scaffolds preventing bacterial infection *in vitro* and *in vivo* (Table 2) (Lu *et al*., 2021).

Osteoarthritis (OA) is a joint disease that causes biological and mechanical disorders. Nonsteroidal anti-inflammatory drugs can reduce symptoms and have no role in disease progression. One of the most significant anionic polysaccharides utilized in scaffolds and drug delivery systems is hyaluronic acid (HA). Because of its better biocompatibility, biodegradability, and chemical modification, HA-based scaffolds used for tissue engineering have previously been intensively investigated (Chircov *et al*., 2018). The present invention describes the use of an HA binding peptide polymer in a hyaluronic acid- (HA-) containing hydrogel (Table 2) (Faust *et al*., 2018). Posttraumatic, HA binding technology can be used to prevent cartilage tissue degradation. *In vivo*, this PEG-collagen binding peptide (COLBP) HABP2-8 arm polymer material can be conjugated to the active

Table 2. Summary of studies reporting on the biomedical effects of biopolymer peptides**.**

Source of biopolymer	Application	Main effect	References
Polyurethane thermoplastic peptide polymer (TPU)	Drug-resistant microbes	Antimicrobial potential peptide polymer-modified TPU has been clinically added, and the solution prevents the spread of bacterial infections related to implant materials and devices	(Lu *et al*., 2021)
Peptide-modified polystyrene-based polymer	Human embryonic stem cell growth and reproduction (hESCs)	The modified peptides were shown to contribute to the attachment activity or proliferation of pluripotent stem cells, as well as to be capable of supporting the long-term development of HUES-7, H7, and DF699. This research facilitates the development of pluripotent and very efficient human pluripotent stem cells	(Yang *et al*., 2021)
HA and collagen binding peptide (COLBP) polymer platform	Treatment of posttraumatic osteoarthritis	Including both young and older mice, treatment with the PEG-COLBP-HABP2-8 arm was found to significantly reduce the expression of inflammatory genes (IL-6, IL-1, and MMP-13) while increasing aggrecan expression. This polymer material may also decrease pain and prevent cartilage degradation	(Faust *et al*., 2018)
Wound dressing made from cross-linked hydrogel tissue (CMCS), poly-y-glutamic acid (y-PGA), and antifibrotic polypeptide (AF38Pep)	Scar healing and prevention (HSP)	HSP significantly decreases scar formation and treats the skin similarly to normal, uninjured skin tissue. This HSP wound dressing provides a potential antiscarring and skin tissue regeneration approach, as well as a novel therapeutic alternative for hypertrophic scars and keloids	(Zhang *et al*., 2021)
Salvia hispanica chia seed bioactive peptides	Antimicrobial	The peptide fraction 3 kDa shows greater antimicrobial activity than chia seed hydrolyzate and the peptide fraction 3–10 kDa, providing a mechanism for use as an antimicrobial agent in medicinal properties	(Aguilar-Toalá *et al*., 2020)
Aloe vera peptide/polypeptide fraction (PPF)	Alleviation of diabetes through maintenance of intestinal permeability by regulating insulin and glucagon-like peptide-1 (GLP-1) levels	In streptozotocin-induced rats, PPF was able to reduce fasting plasma glucose levels with a concomitant increase in insulin levels. Elevated levels of GLP-1 and decreased levels of DPP-IV and zonulin reduce intestinal permeability. Intestinal histopathology also supports the administration of PPF	(Babu *et al*., 2021)
Modification of collagen peptide phosphorylation from fish bone (CP)	Calcium chelating and antioxidant activity	After chelation, the molecular weight and size of CP increased, and modifying its phosphorylation was able to improve CP's calcium binding and antioxidant capacity. This transformation is also tolerant to changes in pH, temperature, and digestive environment	(Luo *et al*., 2022)
Gelatin cryogel bioactive peptide biomimetic BMP-2 and vascular endothelial growth factor (VEGF)	Scaffolding for osteogenesis	Experiments on rat BMSC cultures in vitro showed that scaffolds containing various growth factors might synergistically enhance bone repair. Furthermore, for biomaterial-based noncushioned bone regeneration, this gelatin cryogel platform may perform in a cell-responsive approach	(Lili *et al*., 2022)
Collagen-based hydrogel	Corneal stromal regeneration	Hydrogel-based hydrogels containing neurogenerative medicines are successful in delivering therapeutics to stromal cell regeneration in vitro. This hydrogel may be presented as an innovative implantation strategy that can retain the integrity, transparency, and function of biomaterials while also regenerating corneal stromal tissue	(Xeroudaki *et al*., 2020)

drug, facilitating it reaching the target or injured cartilage tissue as efficiently as possible. The highly variable molecular weight of HA makes assessing its effectiveness in clinical investigations with a wide variety of cases a challenge (Faust *et al*., 2018).

Antifibrotic biomaterials can be used to establish effective fibrosis therapy. According to research, hydrogel lyophilization can produce greater wound dressing material related to its elements as a barrier, moisture absorption and retention, cytocompatibility, and controlled release of bioactive compounds (Mulholland *et al*., 2017). Histological evaluation of wound repair showed that scar healing and prevention biomaterials (HSP) significantly enhanced the regeneration of the epidermis and dermal layer of the skin, as well as neovascularization and development of new skin layers. Research has also found that HSP minimizes scar formation and is compatible with normal injured skin tissue (Table 2) (Zhang *et al*., 2021). Local release of the antifibrotic polypeptide (AF38Pep) and stimulation around the wound site, on the other hand, suggests that the polypeptide has a defensible function in wound dressing materials. Composite wound dressing materials have Young's modulus and elasticity which are applicable for flexibility which is important in specific skin wound areas. The porosity of the wound dressing helps promote swelling and controlled release of the packaged macromolecules within it, as well as enabling cell adhesion and migration. The ideal pore size of the scaffold shown to increase fibroblast migration and promote wound healing is between 20 and 125 μm (Chouhan *et al*., 2019; Yannas *et al*., 2015). Degradation rate, release profile, water vapor transmission rate, water uptake capacity, and surface wettability are also important parameters for wound dressings (Nosrati *et al*., 2021).

Peptides and polypeptides derived from plants are gel materials that have been associated with a wide range of medicinal functions, including the treatment of diabetes. According to a research article, an *Aloe vera* gel peptide with a molecular weight of 29 KDa known as verectin, when combined with polysaccharides, has hypoglycemic activity (Babu *et al*., 2021). The PPF of *A. vera* decreases intestinal permeability and zonulin levels to solve diabetes mellitus by repairing islet cells through the GLP-1/DPP-IV pathway, according to this research.

In general, more than 50 proteins and their four junctions regulate intestinal permeability. Zonulin is one of the proteins involved in the loss of intestinal permeability by binding to the epidermal growth factor, which promotes phosphorylation of zonulin occludens, actually resulting in loss of intestinal permeability (Jayashree *et al*., 2014). The tryptophan-containing peptide polymer has been shown to bind the enzyme DPP-IV, leading to a rise in the quantity of GLP-1 which acts on pancreatic beta cells to secrete insulin through the cAMP/protein kinase A and/or MAPK pathways (Liu *et al*., 2020; MacDonald *et al*., 2002).

Polyphenols and their biomedical effects

Based on particular relevant studies, polyphenols cause a wide range of bioactivities in biomedical applications, including anti-inflammatory, antioxidant, anticancer, hepatoprotective, and anticardiovascular potential (Table 3). Up to this point, there has been a significant amount of *in vitro* research evidence that analyzes the application of polyphenolic biopolymers, alone or even in combination with other polymeric materials, as a strategy for enhancing their efficacy.

Recent studies have demonstrated the use of polyphenolic nanoparticles (NPs), which not only control the formation of new blood vessels but also specifically disrupt the available tumor blood vessels. This explains the significance of polyphenols, which are phytochemicals derived from plants that have antiangiogenic activities (Table 3) (Liu *et al*., 2021). Several important surface receptors implicated in tumor angiogenesis have been investigated, including the VEGF receptor-2, TIE-2, fibroblast growth factor receptor, insulin-like growth factor receptor-1, and epidermal growth factor receptor (previously to identify potential molecular pathways of brain tumor targeting and vascular-specific inhibition) (Anthony *et al*., 2019). Quercetin nanoparticles (Q-NPs) are implicated in VEGFR-2 binding. This is significant since VEGFR-2 activation is a crucial stage in the development of tumor angiogenesis (Tzima *et al*., 2005). Furthermore, blocking angiogenesis by reducing VEGFR-2 signaling has been considered as an effective cancer therapeutic strategy (Mitran *et al*., 2018). As a result, the Q-NP component may decrease angiogenesis by suppressing VEGFR-2 signaling (Liu *et al*., 2021).

Plant polyphenols such as *Hippophae rhamnoides* (HPs60) were extracted using a porous resin, characterized using liquid chromatography mass spectrometry (LCMS), and investigated for colorectal anticancer activity *in vivo* and *in vitro*. For these results, kaempferol, which was investigated in HPs60 using LCMS, is a flavonoid subclass of flavones with significant therapeutic qualities, including antibacterial, antioxidant, anticancer, cardioprotective, and antidiabetic, which are used in cancer chemotherapy (Calderon-Montano *et al*., 2011). miRNAs are implemented to effectively monitor and integrate different biological signaling transduction pathways in normal and pathological processes. As a result of miRNA expression proving abnormal under certain conditions, miRNA is significantly increasingly being implemented as a marker in cancer research, including therapeutic and clinical diagnostic methods.

Three miRNAs were identified as therapeutic targets for HPs60 in this investigation. Interestingly, each target miRNA has a major function in cancer cell development. The HPs60 material promotes the production of Mir-497-5p and miR-195-5p, both of which are known to be downregulated in cancer cells, and their overexpression may impede proliferation, migration, and invasion while also stimulating apoptosis as well as reducing miR-1247-3p expression (Table 3) (Wu *et al*., 2021). Polymeric materials, such as polyphenols, are highlighted for their capacity to inhibit the cell cycle, which is an effective technique for preventing cancer cell proliferation caused by cell cycle dysregulation. Cell cycle control occurs throughout the four eukaryotic cell cycles between G1 and S (phases G1, S, G2, and M).

The polyphenols found in marine algae are higher than those found in terrestrial plants, and they have several other advantages, such as being a more environmentally friendly source of polyphenols because they produce more biomass, require less fresh water, and can be harvested in marine environments where chemical pesticides are generally not used (Table 3) (Murray *et al*., 2018; Buono *et al*., 2014). A latest clinical study in humans using polyphenol-rich seaweed extract (PSE) therapy for 12 weeks resulted in a decrease in total cholesterol levels of about 4%–8% and low density lipoprotein cholesterol levels to about 10%–14% (Hernández-Corona *et al*., 2014; Shin *et al*.,

Table 3. Summary of studies reporting on the biomedical effects of polyphenol biopolymers.

Source of biopolymer	Application	Main effect	References
NP	Glioma treatment	Antitumor activity was shown by quercetin-containing nanoparticles, which inhibited the formation of new blood vessels. This demonstrates that NP reduces tumor development and improves medicine delivery to the target	(Liu *et al*., 2021)
H. rhamnoides L. polyphenols (HPs60)	Anti-colorectal cancer	In vitro and in vivo, HPs60 is beneficial as a natural bioactive component and reveals potential miRNA treatments for colorectal cancer	(Wu *et al*., 2021)
Mango polyphenols (MP)	MicroRNA modulation associated with the PI3K/AKT/mTOR axis in breast cancer cell lines (MCF-12A) and MDA-MB231	MP suppresses inflammation in normal cells and cancer cell growth via regulating the PI3K/AKT/mTOR pathway and related microRNAs	(Arbizu-Berrocal *et al*., 2019)
Fucus vesiculosus seaweed extract polyphenols	Anticardiovascular (cholesterol, triglycerides, glucose, and inflammation)	In this investigation, despite a small rise in HDL cholesterol, seaweed polyphenol extract was able to preserve the major cardiovascular cause. Larger sample numbers are required to confirm clinical relevance and HDL cholesterol reductions	(Murray *et al*., 2021)
White tea extract polyphenols (WTE)	Modulation of the metabolic syndrome, including abnormal lipid metabolism	WTE polyphenols play a vital role in correcting abnormal lipid metabolism in vitro	(Luo *et al*., 2020)
Luteolin from the leaves of Clerodendrum cyrtophyllum Turcz	Antioxidant, anticytotoxicity, antigenotoxic	Luteolin from C. cyrtophyllum leaves has the potential to be developed as a natural antioxidant agent with cytotoxic and antigenotoxic properties, as well as decreased ROS accumulation, release of lactate dehydrogenase, malondialdehyde levels, and increased levels of SOD and glutathione up to procaspase-3 regulation and downregulation of cleaved caspase-3	(Li *et al*., 2020)
Luteolin (LUT) and buddleoside (BUD) from Flos chrysanthemi	Antihypertensive	Administration of LUT and BUD had a synergistic antihypertensive effect in spontaneously hypertensive rats (SHR)	(Lv *et al*., 2013)
Resveratrol Polygonum cuspidatum	Urine markers associated with aging	Resveratrol P. cuspidatum decreased the concentration of N-methyl-2-pyridone-5-carboxamide (2PY) and phenylacetylglycine (PAG), and an abnormally short treatment (seven weeks) was able to indicate the prospective significance of these compounds in experimental animals	(Peron *et al*., 2018)
Resveratrol and green tea extract phytochemicals	Antioxidant and photoprotective activity	The combination of resveratrol and green tea emulgel is used as an additive in herbal-based sunscreen formulations that have a significant sun protection factor value and antioxidants	(Bhattacharya *et al*., 2020)
Grape peel extract contains resveratrol	Antianxiety therapy due to neuroinflammation	Resveratrol, as a potential target for anxiety treatment, may decrease lipopolysaccharide-induced anxiety via inhibiting Yes-associated protein and increase hippocampus autophagy	(Qiuyun *et al*., 2020)

2012; Choi *et al*., 2015). PSE has been demonstrated to lower proinflammatory indicators such as interleukin-6 (IL-6), IL-1, and TNF *in vivo* (Murray *et al*., 2021). Study findings should examine expanding the sample size, evaluating polyphenolic component bioavailability in the digestive system and molecular metabolism, and maybe adding coating polymers to boost the efficiency of these polyphenols.

Aging is a critical objective in the development of therapeutic medications aimed at lowering the incidence of chronic illnesses caused by age, biochemical context, and physiological degradation in the body (Peron *et al*., 2018). Resveratrol is an aromatic chemical obtained from plants which has a wide range of bioactivity and is an effective antioxidant and antiaging agent (Yazhou *et al*., 2020). Following research, resveratrol compounds may be used as food additives as well as functional polymeric materials (Mora-Pale *et al*., 2015). The application of resveratrol *P. cuspidatum* for 49 days resulted in alterations in various biological indicators correlated with aging in the urine of old mice, including decreased 2PY and PAG, metabolite of improved 3-hydroxycebasic acid, and 2,6-hydroxyquinoline. In addition to plants, recombinant microorganisms may be used to bioproduce resveratrol (Braga *et al*., 2018; Sáez-Sáez *et al*., 2020). The shikimate pathway is used to synthesize resveratrol from the aromatic amino acids *L*-phenylalanine (L-Phe) or *L*-tyrosine (L-Tyr) (Kobayashi *et al*., 2021).

CONCLUSIONS, LIMITATIONS, AND FUTURE PROSPECTS

Biopolymers have been highlighted because they offer certain benefits over synthetic polymers in the biomedical sector. Much focus has been given in recent decades to the utilization of renewable resources, and biopolymers are predicted to become promising agents as a new paradigm of ecological protection in the future because even though biopolymers have been widely used in developed countries, there is still a lack of awareness in developing countries about the importance of reducing waste, greenhouse gas emissions, pollution, etc., because biological polymers have limiting factors such as research costs and dissemination that are related to biopolymers. Based on this, the government or other relevant authorities may implement policies to support biopolymer research and activity. Biopolymers offer ecologically friendly qualities, biocompatibility, and biodegradability and have been shown in *in vitro* and *in vivo* tests to be useful in treating some illnesses. These studies all indicate that promoting natural biopolymers and biocomposites not only enhances their physical and chemical features but also enhances their efficacy in a variety of clinical disorders such as cancer, diabetes, aging, and bacterial and viral infections. The bioactive components in biopolymers have a mode of action that increases their efficacy in a variety of clinical diseases.

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CONFLICTS OF INTEREST

The authors report no financial party or any other conflicts of interest in this work.

ETHICAL APPROVAL

This study does not involve experiments on animals or human subjects.

AUTHOR CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the international committee of medical journal editors (ICMJE) requirements/guidelines.

DATA AVAILABILITY

All data generated and analyzed are included within this research article.

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