

# Biomedical Biopolymers, their Origin and Evolution in Biomedical Sciences: A Systematic Review

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## ABSTRACT

Biopolymers provide a plethora of applications in the pharmaceutical and medical applications. A material that can be used for biomedical applications like wound healing, drug delivery and tissue engineering should possess certain properties like biocompatibility, biodegradation to non-toxic products, low antigenicity, high bio-activity, processability to complicated shapes with appropriate porosity, ability to support cell growth and proliferation and appropriate mechanical properties, as well as maintaining mechanical strength. This paper reviews biodegradable biopolymers focusing on their potential in biomedical applications. Biopolymers most commonly used and most abundantly available have been described with focus on the properties relevant to biomedical importance.

**Keywords:** Biodegradable, Biomedical applications, Polymers

## INTRODUCTION

Biopolymers are the types of polymers that are produced by living organisms. In other words they are polymeric biomolecules. This includes plants of many types, such as corn and soybeans, but can also come from different types of trees and even some bacteria. Biopolymers can be classified as follows;

Classified according to the monomeric unit used and the structure of the biopolymer formed [1].

- Polynucleotides i.e. DNA and RNA which are long polymers composed of 13 or more nucleotide monomers.
- Polypeptides which are short polymers of amino acids.
- Polysaccharides, which are linear, bonded polymeric carbohydrate structures.

Depending on their origin they can be classified into [2]:

- Polyesters: Polyhydroxyalkanoates, Polylactic Acid.
- Proteins: Silk, Collagen/Gelatin, Elastin, Resilin, Adhesive, Polyaminoacid, Soy, Zein, Wheat Gluten, Casein, Serum Albumin.
- Polysaccharides (Bacterial): Xanthan, Dextran, Gellan, Levan, Curd Lan, Polygalactosamine, Cellulose.
- Polysaccharides (Fungal): Pollulan, Elsinan, Yeast Glucans.
- Polysaccharides (Plant/Algal): Starch, Cellulose, Agar, Alginate, Carrageenan, Pectin, Konjan, Various Gums.
- Polysaccharides (Animal): Chitin, Hyaluronic Acid.
- Lipids/Surfactants: Acetoglycerides, Waxes, Emulsion.
- Polyphenols: Lignin, Tannin, Humic Acid.
- Specialty Polymers: Shellac, Poly Gamma Glutamic Acid, Natural Rubber, Synthetic Polymers from Natural Fats and Oils.

The United States Congress Office of Technology Assessment classifies them into nucleic acids, proteins, polysaccharides, polyhydroxyalkanoates and polyphenols [3].

Biopolymers are generated from renewable sources and are easily biodegradable because of the oxygen and nitrogen atoms found in their structural backbone. Biodegradation converts them to CO<sub>2</sub>, water, biomass, humid matter, and other natural substances. Biopolymers are thus naturally recycled by biological processes [4].

Biodegradable products are very useful in medical applications. Many of these applications can be found in the medical field and can be roughly divided into four categories:

- Drug delivery systems.

- Wound closure.
- Healing products and surgical implant devices.
- Bioresorbable scaffolds for tissue engineering.

## Collagen

Collagen discovered in 1838 by Payen, is the primary structural material of vertebrates and is the most abundant mammalian protein accounting for about 20–30% of total body proteins [5]. Collagen is synthesized by fibroblasts, which usually originates from pluripotential adventitial cells or reticulum cells. The basic collagen molecule is rod-shaped with a length and a width of about 3000 and 15 Å, respectively, and has an approximate molecular weight of 300 kDa [6].

It is easily absorbable in the body and has very low antigenicity. Moreover, it is non-toxic, biocompatible and biodegradable. It has high tensile strength and high affinity with water [7,8].

## Applications of collagen in biomedical science

**Tissue based device:** Tissue based device like prosthetic heart valves and vascular prosthesis have increased the life expectancy of many cardiac patients with lower risk of infection [6].

**Collagen-based drug delivery systems:** The main application of collagen films is as barrier membrane [6]. Collagen film/sheet/disc has been used for the treatment of tissue infection, such as infected corneal tissue or liver cancer. Soluble ophthalmic insert in the form of a wafer or a film was introduced as a drug delivery system for the treatment of infected corneal tissue using a high dose of antibiotic agents, such as gentamycin and tetracycline. Collagen film and matrix have been used as gene delivery carriers for promoting bone formation [6].

**Collagen sponges:** Collagen sponges are very useful in the management of severe burns and as a dressing for severe types of wounds. Collagen dressings are prepared in a variety of different forms including, sponges, membrane sheets and powder, having essential biological properties important for such application [6].

**Gel, hydrogel, liposomes-collagen:** One of the successful applications of collagen for the controlled delivery systems is collagen-based gel as an injectable aqueous formulation. Collagen hydrogel was also used as gene delivery carriers [6].

**Nanoparticles/nanospheres:** The nanoparticles or nanospheres based biodegradable collagen are thermally stable, readily achieve

their sterilization. Because of its small size, a large surface area, high adsorptive capacity and ability to disperse in water to form a clear colloidal solution, collagen-based nanoparticles have demonstrated their potential to be used as a sustained release formulation for anti-microbial agents or steroids [6]. Nanoparticles have been used as a parenteral carrier for cytotoxic agents and other therapeutic compounds, such as camptothecin [9] and hydrocortisone [10].

**Collagen-based systems for tissue engineering:** Collagen based implants have been widely used as vehicles for transportation of cultured skin cells or drug carriers for skin replacement and burn wounds. Collagen has been used as bone substitute due to its osteoinductive activity. Collagen has been used as implantable carriers for bone inducing proteins, such as bone morphogenetic protein 2 (rhBMP-2) [6].

**Collagen as a haemostat:** Collagen achieves rapid coagulation of blood through its interaction with the platelets and providing a temporary framework while the host cells regenerate their own fibrous stroma. The use of collagen based haemostats has been proposed for reducing blood loss in generalized bleeding in a wide number of tissues and management of wounds to cellular organs such as liver or spleen [6].

### Gelatin

Gelatin is a water soluble proteinaceous substance prepared by the destruction of the tertiary, secondary and to some extent the primary structure of native collagens, by the partial hydrolysis of collagen derived from the skin, white connective tissue and bones of animals [11]. Gelatin differs from other hydrocolloids because most of them are polysaccharide, whereas gelatin is a digestible protein containing all the essential amino acids except tryptophan [12].

Gelatin can be made from many different sources of collagen. Cattle bones, hides, pig skins, and fish are the principle commercial sources. Gelatin is used as a foaming, emulsifying, and wetting agent in food, pharmaceutical, medical and technical applications due to its surface-active properties [13].

### Chitosan

Chitosan is a derivative of the natural polysaccharide, chitin. Chitin was first isolated and characterized from mushrooms, by French chemist Henri Braconnot in 1811 [14]. It is the second most abundant biopolymer in the world. Except celluloses, chitin is the most abundant polysaccharide in nature, being the main component of the exoskeleton of crustaceans and insects, also occurs, in nematodes and in the cell wall of yeast and fungi [15,16]. Chitosan is excellent in biocompatibility; high bioactivity; biodegradability; selective permeability; polyelectrolyte action; antimicrobial activity; ability to form gel and film; chelation ability and absorptive capacity [17]. These peculiar properties provide a variety of applications to Chitosan, such as: drug carrier for controlled release [18], anti-bacterial [19,20] and anti-acid [21]; inhibits the bacterial plaque formation and decalcification of dental enamel [22,23], promotes Osteogenesis [24], fat absorbent action and promotes the healing of ulcers and lesions [25,26].

**Chitosan as an anti-oxidant:** Chitosan has an in vivo stimulatory effect on both nitric oxide production and modulates peroxide production [27]. Neutrophil activation was inhibited by administration of chitosans with low molecular weight and oxidation of serum albumin commonly observed in patients undergoing haemodialysis, resulting in reduction of oxidative stress associated with uremia [28].

**Chitosan and drug delivery:** It has potential to improve drug absorption and stabilization of drug components to increase drug targeting. In addition, chitosan can protect DNA and increase the expression period of genes. Chitin or chitosan derivatives, which were conjugated with some kinds of anticancer agents, can execute better anticancer effects with gradual release of free drug in the cancer tissues [29].

**Chitosan as an anti-inflammatory agent:** Chitosan is confirmed to partially inhibit the secretion of both IL-8 and TNF- $\alpha$  from mast cells, demonstrating that water-soluble chitosan has the potential to reduce the allergic inflammatory response. Chitosan promotes phagocytosis and production of osteopontin and leukotriene B by polymorphonuclear leukocytes, production of interleukin-1, transforming growth factor b1 and platelet-derived growth factor by macrophages, and production of interleukin-8 by fibroblasts, enhancing immune responses [29].

**Chitosan composite for tissue engineering:** Chitosan and hydroxyapatite are one of the best bioactive biomaterials in bone tissue engineering [30]. Different types of Marine source polysaccharides are used for management of bone diseases like Osteoporosis and arthritis [31,32]. As a functional wound dressing and in order to create a moist environment for rapid wound healing, a hydrogel sheet composed of a blended powder of alginate, chitin/chitosan and fucoidan has been developed [33]. It is highly biocompatible, biodegradable, porous structure, suitable for cell ingrowth, osteoconduction and intrinsic antibacterial nature, chitosan has been developed considerably in biomedical applications [34]. Its application includes cartilage tissue engineering [35], wound healing and orthopedic applications [36]. Degradable polymeric implants eliminate the need for a second surgical operation [37]. Chitosan/Hydroxyapatite composite materials show promise in mimicking the organic portion as well as the inorganic portion of natural bone [37].

**Chitosan as an anti-microbial agent:** Chitosan shows antimicrobial action in a great variety of microorganisms, including algae, fungi and bacteria. It has shown antimicrobial activity against gram-positive bacteria and various species of yeast [38,39].

The chitosan gel; derived from dilution in acetic acid is suggested as a preventive and therapeutic material for dental caries [40].

### Cellulose

It is the most abundant naturally occurring polymer of glucose, found as the main constituent of plants and natural fibers such as cotton and linen. Some bacteria (e.g., *Acetobacter xylinum*) can also synthesize cellulose. Plant cellulose is chemically identical to Microbial or bacterial cellulose, although possessing different macromolecular structure and physical properties [41].

Cellulose has an organic formula  $(C_6H_{10}O_5)_n$ , a polysaccharide having a linear chain of several hundred to over ten thousand  $\beta$  (1 $\rightarrow$ 4) linked D-glucose units [42]. Cellulose with its derivatives is environmentally friendly. The most important cellulose fibers in medical applications are natural cotton fibers and different regenerated (man-made) cellulose fibers such as viscose, modal, and lyocell [43].

**Devices for Controlled Drug Delivery:** In solid tablets, cellulose ether is used which allows a swelling-driven release of the drug as physiological fluids come into contact with the tablet itself. The cellulose ether on the tablet surface starts to swell, forms chain entanglements and a physical hydrogel. As swelling proceeds from the surface to the glassy core of the tablet, the drug progressively dissolves in water and diffuses out from the polymer network [44,45].

**Scaffolds for Regenerative Medicine:** Due to the excellent biocompatibility of cellulose and its good mechanical properties the use of cellulose and its derivatives as biomaterials for the design of tissue engineering scaffolds has been increasing [46-48].

**Wound Dressings:** Bacterial cellulose (BC) has been widely investigated for wound healing due to its purity and high water retention capacity [49].

### Xylan

Xylan, a hemicellulose largely found in nature, is considered the second most abundant polysaccharide after cellulose. Xylans are the main hemicelluloses in hardwood and they also predominate in

annual plants and cereals making up to 30% of the cell wall material and one of the major constituents (25–35%) of lignocellulosic materials [50-52].

Xylan has been considered as a suitable raw material to produce colonic drug delivery systems as it is biodegraded by enzymes produced by the colonic microflora [53-55]. Physiological effects of Xylans: Viscous character of the fiber polysaccharides in cereals leads to the faecal bulking effect and lowering of blood cholesterol and decrease of postprandial glucose and insulin responses. Water extractable polysaccharides of cereals are claimed to alleviate alcoholic liver disorders. Arabino glucurono xylans possessing immunostimulating activities have been isolated from some herbal plants. Some of these xylans also show anti-phlogistic effect. Xylan rich hemi-celluloses extracted from plant waste such as bamboo leaves, wheat straws and corn stalks have been reported to inhibit the growth rate of sarcoma 180 and other tumours, probably due to the indirect stimulation of the non-specific immunological host defense. T-lymphocytes and immunocytes are activated by Carboxymethylated xylan rich wood hemicelluloses [56].

Pentosan polysulfate (PPS) has been known as an anti-coagulant and usually derived from beechwood glucuronoxylan. The PPS in gel form can be used in treatment of infusion thrombophlebitides [57].

**Alginates:** One of the most abundant biosynthesized materials, water soluble polymers extracted from brown seaweed. Alginates are hydrocolloids [58]. Alginate is used to support matrix or delivery system for tissue repair and regeneration. Because of its biocompatibility, biodegradability, non-antigenicity and chelating ability, alginate is widely used in a variety of biomedical applications including tissue engineering, drug delivery and in some formulations preventing gastric reflux. It is an approved polymer by U.S. Food and Drug Administration (FDA), thus alginate has become one of the most important biomaterials for diverse applications in regeneration medicine, nutrition supplements etc [59-62]. Alginates are also widely used for impression making in the dental clinic because of its ease in handling [63].

**Wound dressings:** A mix of sodium and calcium alginate acts as a foundation for alginate dressings used for haemostasis and wound closure. They provide a moist environment at the wound bed, achieve haemostasis and absorb exudate [64]. They also reduce wound pain, lower the bio-burden of the wound, absorb proteinases and reduce odour [65,66]. Alginate-based wound dressings such as, hydrogels, electrospun mats and sponges offer many advantages including gel-forming ability upon absorption of wound exudates and haemostatic capability [67,68].

**Drug delivery:** Alginate is widely used as a carrier to immobilize or encapsulate drugs, for its biocompatible and biodegradable nature [69,70].

### Carrageenan

Carrageenan is derived from a number of seaweeds of the class Rhodophyceae. Carrageenan is a generic name for a family of gel-forming and viscosifying polysaccharides. Carrageenan is a sulfated polygalactan with 15 to 40% of ester-sulfate content.

**Anticoagulant and antithrombotic activity:** The principal basis of the anticoagulant activity of carrageenan appears to be an anti-thrombic property. The mechanism underlying the anticoagulant activity of carrageenan involves thrombin inhibition. There is either anti-thrombin potentiation via heparin co-factor II (HC-II) and/ or a direct anti-thrombin effect [71].

**Antiviral activity:** Carrageenan is a selective inhibitor of several enveloped viruses, including such human pathogens as human immunodeficiency virus, herpes simplex virus (HSV), human cytomegalovirus, human rhinoviruses and others [72,73]. Carrageenan acts primarily by preventing the binding or the entry of virions into cells [74].

Carrageenan is considered to be a good substitute for gelatin (animal-

based product) in hard and soft gel capsules. Its incorporation in glycerin-water mixture masks the chalkiness of antacid gels. It can be used in both topical bases and suppository bases. It acts as a thickener and binder in dentifrices and prevents liquid-solid separation [75].

### Gum Arabic

Gum Arabic is a dried, edible, gummy exudate from the stems and branches of *Acacia Senegal* and *Acacia seyal* that is rich in non-viscous soluble fiber. In folk medicine GA is used externally to cover inflamed surfaces and internally for the treatment of inflammation of intestinal mucosa [76]. Studies have claimed that GA possesses antioxidant and nephroprotectant properties. However, these findings are not universally accepted. Due to its physical properties, it reduces glucose absorption, increases fecal mass, bile acids and has the potential to beneficially modify the physiological state of humans [77]. Some studies report Gum Arabic having growth inhibitory activity of certain pathogenic species (causal agent of tooth decay or agent involved in the plaque), such as *Porphyromonas gingivalis* and *Prevotella intermedia* [78]. As per the studies GA could improve dental remineralization and inhibit the formation of plaque, acting as a potential preventive agent in the formation of caries. Such effects are attributed to the high salt content of  $Ca^{+2}$ ,  $Mg^{+2}$  and  $K^{+}$  of polysaccharides in GA, and the effect of the gum in the metabolism of Ca and possibly phosphate [79].

Incorporation of Gum Arabic improves the hardness of gypsum products. Small amount of Gum Arabic plus calcium carbonate added to the hemihydrate can reduce the amount of water required for mixing of both plaster and stone [80].

### Xanthan Gum

Xanthan gum is a natural polysaccharide produced by the bacterium *Xanthomonas campestris*. The primary structure of xanthan consists of repeating pentasaccharide units consisting of two D-glucopyranosyl units, two D-mannopyranosyl units and one D-glucopyranosyluronic unit [81]. The thickening ability of xanthan solutions is related with viscosity; a high viscosity resists flow. Xanthan solutions are pseudoplastic, or exhibit shear thinning characteristics, and the viscosity decreases with increasing shear rate.

Xanthan gum is widely used in toothpastes and cosmetics [82]. It can be easily extruded from the tube. It also ensures that toothpaste will keep a stable stand on the brush. The shear thinning characteristics also improve the dispersion on and the rinsing from the teeth. Thickened toothpaste with xanthan gum has a bright, shiny cord with short flow behaviour. In emulsions or suspensions for pharmaceutical use xanthan gum prevents the separation of insoluble ingredients [82].

### Pectin

Pectin is a structural heteropolysaccharide contained in the primary cell walls of terrestrial plants. Pectin consists of a complex set of polysaccharides that are present in most primary cell walls and particularly abundant in the non woody parts of nearly all terrestrial plants. Commercial pectins are almost exclusively derived from citrus peel or apple pomace, both of which are by-products from juice manufacturing units. Pectin is thought to consist mainly of D-galacturonic acid (GalA) units, joined in chains by means of  $\alpha$ -(1-4) glycosidic linkage [83]. Pectin is used for making mucoadhesive patches in combination with carbopol and chitosan. It acts by coming in intimate contact with tissues and entanglement of polymer and mucin chains and formation of weak bonds between chains. Pectin acts as a natural prophylactic substance against poisoning with toxic cations. Pectin is effective in removing lead and mercury from the respiratory organs and gastrointestinal tract. Pectin improves the coagulation and thus useful in controlling haemorrhage [83].



Pectin is helpful in treatment of overeating as it reduces the rate of digestion by immobilizing food components in the intestine, resulting in less absorption of food [83].

Pectin hydrogels have been used in tablet formulation as a binding agent and have been used in controlled release matrix tablet formulations. Pectin is presently being considered as a carrier material in colon specific drug delivery system [84].

Certain pectins showed some anti-inflammatory properties *In vitro*, a promising and favourable trait in medical device tuning. Pectins are nowadays under enthusiastic investigation in the biomaterial field as novel candidates for soft and hard tissue engineering and dental titanium coating as it promotes *in vitro* immunological responses [84].

## Hyaluronic Acid

Hyaluronic acid is widely distributed in extracellular matrix and the joint liquid of mammals and approved for injections by the Food and Drug Administration (FDA) [85]. It is a biocompatible mucoadhesive polysaccharide with negative charge and is biodegradable. The first medical application of hyaluronan for humans was as a vitreous substitution/replacement during eye surgery in the late 1950s. Hyaluronic acid polymers are used in the preparation of gels for delivery of drugs to eye and installation into other cavities. Along with other polymers like alginate, HPMC (Hydroxypropyl methyl cellulose), poloxamers etc. they can be used for achieving the desired property in drug delivery systems [86]. Corneal shields based on Hyaluronic acid have demonstrated prolonged steroid delivery, with a consummate smoothing of dosage profile [87]. Other applications of hyaluronic acid as reviewed by Price et al., [88] are as follows: (i) Wound healing by extracellular regeneration; (ii) Epithelial regeneration; (iii) Topical treatment of dry eye syndrome [89] and Sjögren's syndrome [90]; (iv) as a viscosity agent in pulmonary pathology for achieving alveolar patency [91]; (v) Commercial preparation available for intra-articular injection; (vi) As a filler in rejuvenative medicine for wrinkles and cutaneous lines. Viscosupplementation with Hyaluronic acid products helps to improve the physiological environment in an osteoarthritic joint by supplementing the shock absorption and lubrication properties of osteoarthritic synovial fluid. The rationale for using viscosupplementation is to restore the protective viscoelasticity of synovial hyaluronan, decrease pain, and improve mobility [92]. Esterified hyaluronic acid has also been used to prevent bacterial adhesion to dental implants, intraocular lenses, and catheters [93]. Hyaluronic acid is an appropriate choice for a matrix to support dermal regeneration and augmentation. As a result of its ability to form hydrated, expanded matrices, Hyaluronic acid has also been successfully used in cosmetic applications such as soft tissue augmentation [94].

## CONCLUSION

Biopolymers are naturally occurring materials formed during the life cycles of green plants, animals, bacteria and fungi. Biopolymers include animal protein-based biopolymers such as wool, silk, gelatin and collagen and polysaccharides such as cellulose, starch, carbohydrate polymers produced by bacteria and fungi. Biopolymers, especially the carbohydrate origin, have been found very promising for biomedical application in various forms. Because of its low toxicity, biodegradability, stability and renewable nature. Biopolymers are choice of research as excipient. This review discusses some of the most common biopolymers used as excipient in biomedical science.

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