Chitin and Chitosan: Sustainable, Medically Relevant Biomaterials

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Abstract: The polysaccharides chitin and chitosan are made up of monomer units of the amino sugars D-glucosamine and *N*-acetyl-D-glucosamine. The ratio of these two monomers dictates whether the polysaccharide is considered chitin or chitosan. Both polymers have unique properties and have uses in several diverse applications. In nature, chitin and chitosan primarily play a structural role. When purified from their producing organism, these polymers exhibit useful structural, chemical and biological properties. Chitin and chitosan have been used in several applications including biomedicine, food additives, cosmetics, and more. The charged chitosan polymer is especially effective in biomedical applications, as it has been demonstrated to possess antimicrobial properties. This review explores the properties of chitin and chitosan and how these biopolymers are used in a variety of healthcare and other applications.

Keywords: Chitin, chitosan, medical device, biomaterial, N-acetyl glucosamine, seafood waste.

INTRODUCTION

Chitin is the second most abundant polymer in nature, after cellulose. Chitin is so abundant because it is widely distributed in nature as the material that makes up exoskeletons of insects and crustaceans and is also a component of fungal cell walls [1]. The component monosaccharide of chitin is *N*-acetyl-*D*-glucosamine (NAG, or GlcNAc) joined together by β-1→4 linkages [2,3]. In the quest for sustainable alternatives to chemically synthesized plastics and materials, chitin is commanding more notice due to its unique properties. As a structural polysaccharide in nature, chitin has mechanical strength and other favorable properties, making it a suitable alternative to many plastics for applications, *e.g*. sutures. Chitin and derivative polysaccharides are also good materials for medical applications due to their biocompatibility and antimicrobial (at the very least, bacteriostatic) properties. Specifically, chitosan, a chitin-based polysaccharide in which the amino sugar monomers are deacetylated (*i.e.,* D-glucosamine) possesses a charge that can enhance its biological properties as an antimicrobial and/or protective material.

Chitin is generally classified as a polymer of NAG, but it does contain D-glucosamine monomer groups (up to 50 mole %). If the NAG/D-glucosamine copolymer contains more than 50% deacetylated monosaccharide, the resulting polymer is termed chitosan [4]. As a result, chitosan has many important biological and chemical properties. With a net positive charge, chitosan can complex with many important biological molecules, thus allowing for adsorption. Chitosan can recruit important bioactive molecules to a wound or implant site, making it a potentially valuable biomaterial for tissue engineering and wound healing [5,6].

Chitin and chitosan, like many bio-based materials, are considered to be multifunctional. For example, chitin is a load-bearing exoskeleton in arthropods, a means of environmental protection and a water barrier (4). This inherent multifunctionality of these polysaccharides suggests that they can be important bio-based alternatives to materials in a variety of applications. We can seek applications that take advantage of the structural capabilities of chitin and also applications that utilize the water barrier and environmental protection properties of chitin/chitosan.

THE BIOCHEMISTRY OF CHITIN SYNTHESIS

There exists conserved cellular machinery in all chitin-synthesizing organisms for conversion of sugars to linear chitin [7-9]. When chitin is polymerized, the chains are secreted extracellularly, assembled into structures called microfibrils and further organized. Depending on the organism doing the chitin synthesis and organization, extracellular chitin can ultimately take the form of cell walls (fungi), cuticles (arthropods) or peritrophic matrices. Also, depending on the organism, different cell types can synthesize chitin, such as vegetative or sporulating fungal cells [7] and epidermal, tracheal and midgut cells in insects [9].

As implied above, the general chitin biosynthetic pathway is conserved and involves the biochemical conversion of various sugars (*e.g*., glucose, trehalose, etc.) to the NAG polymer [8]. Figure **1** shows a schematic of a general chitin biosynthetic pathway. Typically, the carbon source used for chitin synthesis is

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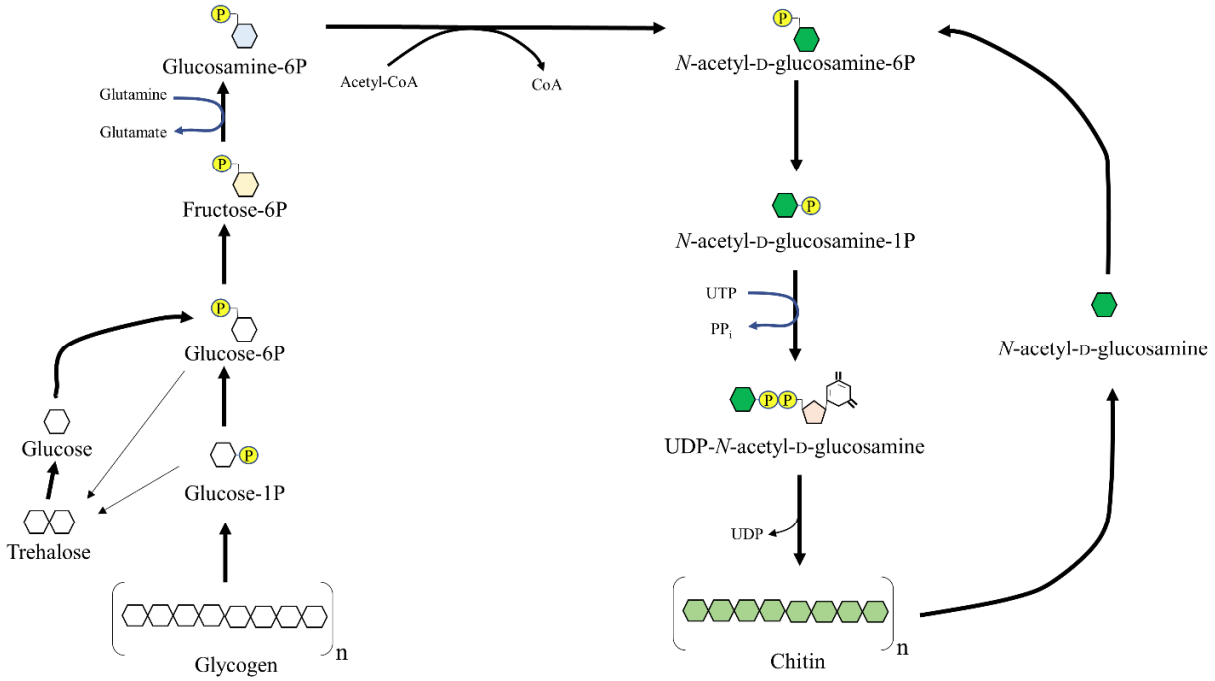

Figure 1: General chitin biosynthesis and degradation pathways.

glucose. Carbon storage compounds like trehalose or glycogen can also be used. Fructose-6P is converted to glucosamine-6P using a transaminase with glutamine as the donor of the amino group. Acetyl-CoA provides the acetyl group to synthesize *N*-acetyl-D-glucosamine-6P. The species that acts as the precursor for chitin synthesis (donor of NAG) is UDP-*N*-acetyl-D-glucosamine. Synthesis of chitin, like the syntheses of almost all polysaccharides, proceeds with a nucleotide diphosphate sugar as the monosaccharide subunit donor [10]. Using nucleotide diphosphates as monosaccharide "carriers" can serve as both a source of energy for chemical bond transfer and a method for delivering precursors to nascent polysaccharides in an accurate fashion [11]. The proposed mechanism for chitin synthesis suggests that the monosaccharide is transferred from UDP-*N*-acetyl-D-glucosamine to the non-reducing end of the growing chitin chain [8]. However, without structural data on chitin synthase enzymes, the mechanism of action generally consists of speculation.

THE STRUCTURE OF CHITIN

Chitin is synthesized by different organisms in one of three different configurations: α-chitin, β-chitin and γ-chitin. Individual chains are arranged in an antiparallel configuration in α-chitin. In β-chitin, the chains are arranged in parallel. γ-chitin is a mixture of both α- and β-chitin [4,11,12]. Figure **2** shows a schematic of the arrangement of the different configurations of chitin. The most abundant form of chitin on earth is α-chitin; it is found in the exoskeletons of lobster, crab and shrimp, as well as fungal cell walls. Chitin in the β configuration can be found in squid pens, associated with proteins. In both α- and β-chitin, groups of chains are organized in sheets, which are held together by intra-sheet hydrogen bonds. In α-chitin, inter-sheet hydrogen bonding has also been demonstrated to occur [3].

In crustacean shells, chitin is complexed with proteins, minerals and other substances and is tightly packed. This gives the shell the strength required to serve as a load-bearing exoskeleton. Chitin in shells is packed into nanofibrils and surrounded by proteins. These protein coated nanofibrils are then packed together to form fibers. Fibers are bundled into sheets or layers, which are stacked according to the "twisted plywood principle" [13]. In short, planar layers of fibers are stacked up helicoidally in a formation that is also termed a Bouligand structure [4]. Stacks of fiber layers are packed on top of each other to form a layered cuticle, which makes up the exoskeletal elements of the crustacean shell [13].

PURIFICATION OF CHITIN AND CHITOSAN

In nature, chitin is complexed with other compounds. To purify and isolate chitin from biological

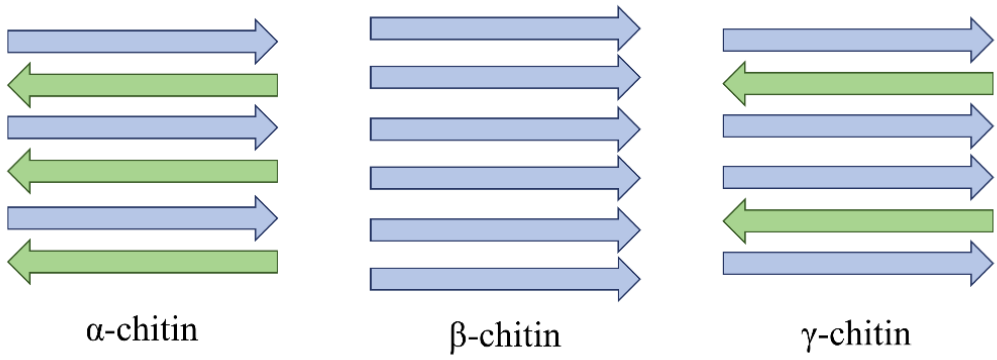

Figure 2: The general organization of α-, β-, and γ-chitin structures. Each colored arrow represents a single chitin chain.

sources, one of several protocols would need to be undertaken. Chitin is present in marine crustaceans like crab, shrimp and lobster at mass percentages of up to 75%. These sources also happen to be food sources that are landed in various ports around the world in millions of metric tons or more per year (http://www.fao.org/fishery/facp/USA/en). In order to access the edible portion of these animals, the chitin-rich exoskeleton, which is about 40-50% of the total mass of the animal [14], is removed. Seafood processing plants perform the removal of shells and then discard the empty shells. The waste shells are often dumped in landfills or back into the sea. Shellfish waste management is a significant problem faced by the fishing and processing industries. Prior to extraction of chitin, the shells are washed, dried and crushed or ground into small pieces. Traditionally, chemical methods of chitin purification have been used to isolate the polysaccharide. For crustacean shells, removal of protein and minerals is undertaken. For deproteinization, the shell biomass is treated at high temperatures (65 – 100°C) by a strong base, typically a 1 M aqueous solution of base, like sodium hydroxide. The most abundant mineral complexed with crustacean shells is calcium carbonate, and this is removed by acid treatment. The acid treatment consists of soaking in moderate to high strength acid like hydrochloric acid. The chemical method of chitin extraction is effective and results in a high purity preparation of chitin. However, this treatment regime results in large volumes of high- or low-pH wastewater, which must be treated before disposal. This effluent treatment may significantly increase the cost of chitin preparation [15]. Also, such harsh treatments can have detrimental effects on the extracted chitin. Strong acid treatment can adversely affect the molecular mass and degree of acetylation of chitin, *i.e.*, depolymerization and deacetylation could occur [16,17]. For a more sustainable, less toxic treatment of crustacean shells, biological methods can be employed to extract chitin. For protein removal, proteolytic bacteria can be used. The cultivation of bacteria like *Pseudomonas* spp., *Serratia* spp. or *Bacillus* spp., among others, in the presence of ground lobster, crab or shrimp shells, results in significant proteolysis and subsequent removal of protein from the shell biomass. Acids are still used in the biological method of calcium carbonate removal. However, lactic or acetic acid producing bacteria can be cultivated with shell biomass, and the organic acid produced by the bacteria reacts with the calcium carbonate to produce calcium lactate. The main result is the removal of the minerals, producing a significantly purer chitin from the shell biomass. In prior studies of biological chitin purification treatments, demineralization and deproteinization efficiencies were observed to be as high as 97%, but generally between 70 and 88% [15].

PROPERTIES OF CHITIN

Many different properties of chitin and chitosan are determined by the extent of acetylation of the polysaccharide. Chitin, especially α-chitin, is not soluble in aqueous liquids, whereas chitosan is soluble in certain acid mixtures [5]. Solvent penetration in the crystal structure is possible in β-chitin, resulting in swelling of the material due to the uptake of liquid [18]. There are a small number of studies that have examined the material strength of chitin and chitosan films. Tomahita and Ikada [19] examined the strength of buffer-swollen chitin and chitosan films. This group demonstrated that fully deacetylated chitosan exhibited the highest material strength under these conditions, but ~75% deacetylated chitosan exhibited the largest elongation to break percentage. Foster *et al.* [20] showed that 72% deacetylated chitosan exhibited the highest strength. It should be noted that the overall elongation to break values of the films examined in this work were significantly lower than those of the buffer-swollen films. However, after uptake of water, the

Table 1: Chemical Modifications to Chitosan Matrixes

Modification	Functional group modified[a]	Purpose for modification (if known)	Reference
N-phthaloylation	$-NH_2$	Increase of solubility	[29]
Dendronized chitosan-sialic acid hybrids	$-NH_2$	Increase of water solubility	[30]
Methylthiocarbamoyl and phenylthiocarbamoyl derivatization	$-NH_2$	Metal ion selectivity	[31]
Lactic/glycolic acid-chitosan hydrogels	$-NH_2$	Crosslinking (stronger interactions)	[32]
Chitosan-gadopentetic acid complex	$-NH_2$ (-OH?)	Production of gadolinium loaded nanoparticles for intratumoral injection	[33]
CdS quantum dots chitosan bicomposite	$-NH_2$ ($-NHCH_2COOH$?)	Improvement of solubility and stability	[34]
Nanocomposites	Any	Polymer blending and production of useful composites	[3,5,22]

[a]Functional groups of chitin and chitosan: -OH = hydroxyl group, $-NH_2$ = amino group, $-NHCH_2COOH$ = *N*-acetylamino group.

chitosan films displayed comparable elongation to break values as compared to those used by Tomahita and Ikada [19].

Many of the unique chemical properties of chitin and chitosan originate from the amino and *N*-acetylamino groups attached to each sugar monomer. These groups are reactive and can facilitate derivatization and crosslinking, among other reactions and modifications. Table **1** lists several modifications of chitin and chitosan that have been attempted in previous works. There is extensive hydrogen bonding between the amino, *N*-acetylamino and hydroxyl groups of each monomer in the chitin or chitosan chain, which results in a rigid crystalline lattice and an overall strong structure [19]. Also, due to the presence of these different functional groups, chitin is capable of acting as a chelator for many different transitional metal ions [5]. These groups can even facilitate adsorption of cells and proteins, and is thus, an ideal material for tissue engineering scaffolds. Also, chitin and chitosan scaffolds have been shown to enhance certain biological activities like drug delivery and have demonstrated antibacterial properties [21]. Like many bio-based polymers, chitin and chitosan are biocompatible and biodegradable in the body [5].

APPLICATIONS OF CHITIN AND CHITOSAN

Due to their unique and diverse properties, chitin and chitosan have been used for a myriad of applications. In particular, the biological properties of chitosan indicate that it is a useful material for biomedical and biotechnological applications. Table **2** lists a few applications for chitin and chitosan.

As one can imagine, different applications require different properties of chitin and chitosan. Much of this depends on the degree of *N*-acetylation. Chitin is biodegradable and can be formed into all types of matrices, including fibers, gels, and films. Studies have shown chitin to be suitable for bone and wound tissue engineering applications. Chemically modified chitin (carboxymethyl chitin and phosphoryl chitin) scaffolds

Table 2: Applications of Chitin and Chitosan

Application	Specific role(s) of chitin/chitosan	References
Tissue engineering	Osteoblast attachment; bone growth	[21,22,25]
	Cartilage growth/replacement	[34,35]
Wound dressing	Burn treatment	[5,23,24]
	Artificial skin	[4,22]
Cosmetics	Skin and hair care; sunscreen	[5,22]
Food additive	Emulsifying agent; thickener	[5,22]
Agricultural	Fertilizer; seed coating	[5,22]

have been shown to be good for bone tissue engineering [21]. The presence of hydroxyapatite in mixture with chitin has been shown to maximize bone growth [4]. Complexing of calcium phosphate with chitin and chitosan has also been shown to be favorable for osteoblast attachment [3,5]. Chitin and chitosan have also been used in cartilage tissue engineering. Previously, cartilage engineering strategies had not been able to regenerate long-lasting cartilage tissue [5]. However, recent studies have made significant progress on this, using chitosan composite scaffolds. It should be noted that glucosamine, while a monomer making up a significant portion of most chitin or chitosan polysaccharides, is also a component in human tissue. Recent studies on cartilage engineering using chitosan composite scaffolds showed that the material is biocompatible, amenable to cell proliferation and, using a specialized casting and freeze-drying technique, is able to regenerate tissue cartilage [22]. Chitin scaffolds have the ability to maintain chondrocyte morphology and can preserve their capability of cell-specific extracellular matrix production.

Chitin and chitosan have been shown to have accelerating effects on the wound healing process. Fibroblast activation, cytokine production, stimulation of type IV collagen biosynthesis were demonstrated when chitin and chitosan were used in wound healing applications [21]. Chitosan has been shown to possess antimicrobial and antifungal properties, but the exact mechanisms are unknown. It is thought that the charged surface of chitosan promotes an alteration of the cell surface charge thus causing an agglutination of bacteria. Also, chitosan is predicted to cause alteration in cell membrane permeability. In animal studies, chitosan and derivatized chitosan bandages were shown to be effective in promoting wound healing [3,23]. Promotion of macrophage nitric oxide (NO) production was also observed when chitin and chitosan materials were used in conjunction with wound healing. This promotion of NO production was attributed to the NAG subunit of chitin and chitosan. *N*-acetyl-D-galactosamine was found to not promote this effect [24]. Chitosan, as it has demonstrated biocompatibility, has also been explored as a substratum for artificial skin replacement [5,25]. Again, chitosan composite materials (e.g. chitosan/alginate or chitosan/collagen) have been used as seed materials for this process [25].

The bioactive nature of chitin and chitosan has also been exploited for use in cosmetics. Chitosan is a favorable ingredient because it is one of the few natural cationic polymers that becomes viscous when neutralized by acid. Also, chitin and hair keratin are complementary to each other, owing to their opposite electrical charges. The ability of chitosan to bind to hair suggests its efficacy in hair care products [5]. Chitin and chitosan composites have been used as sunscreen, as well, with the added attribute of chitosan as an antimicrobial additive [22]. Both chitin and chitosan have been examined as ingredients in chewing gum, mouthwash and toothpaste. Again, the demonstrated antibacterial and antifungal properties of chitosan can be used to promote oral healthcare. However, also chitosan salts can mask unpleasant tastes of certain toothpaste additives and can also bind certain fillers and other ingredients [5]. Encapsulation in chitosan nanoparticles has been shown to reduce the loss of volatile fragrance compounds, which is a key development in cosmetics technology [22].

The properties of chitosan also give it application in other, non-healthcare industries. Its polycationic nature allows it to be used as a flocculant in the water treatment, textile and paper industries [26,27]. Chitosan is very similar to cellulose and promotes strong bonding with cellulose, thus strengthening paper sheets [22]. A type of chitin called Microcrystalline chitin (MCC) can be used as a food additive for emulsification and thickening. As alluded to in the introduction, chitin can be used as a fertilizer. In addition, chitin-coated seeds were shown to promote growth-accelerating/enhancing effects [5]. Chitosan nanoparticles have also been used (applied by spraying on plantlet leaves) to slow nutrient loss in developing seedlings [22].

OUTLOOK

Chitin is an abundant and useful biomolecule. The principal challenge for chitin as an alternative to synthetic materials in biomedical industries is the ability to purify the polysaccharide from its sources. The sources are ever present, as people continue to eat crustaceans like crab, lobster, and shrimp, which means companies are going to continue to process these animals for consumption. The effective utilization of chitin can potentially solve many problems: (i) the mitigation of waste disposal for the shellfish industry, (ii) increased availability of a versatile biomaterial, (iii) production of an environmentally friendly polymer that can act as an alternative for synthetic polymers. For establishment of biorefineries, there are typically two main price points that drive up the cost, compared to petrochemical or synthetic methods: raw material costs

and product separation from non-product biomass. To the first point, waste shell biomass is comparable in cost to lignocellulosic biomass [27]. More research must be done on the second point, even though chemical methods of chitin extraction from shell biomass have been used for decades. Currently, research groups are exploring bio-based chitin extractions. Further work is needed to provide convincing scale-up efforts to establish shell biorefineries for large-scale chitin production. These biorefineries can provide added economic benefits to regions that have traditionally landed large quantities of edible shellfish.

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