

# Chitin and Chitosan

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Chitin and its derivative chitosan are highly abundant polymers in nature, appearing in both the shells and exoskeletons of various marine and non-marine species. Since they possess favorable properties, such as biocompatibility, biodegradability, non-toxicity, and non-immunogenicity, they have gained recent attention due to their enormous potential biomedical applications. The polycationic surface of chitosan enables it to form hydrogenic and ionic bonds with drug molecules, which is one of its most useful properties. Because chitosan is biocompatible, it can therefore be used in drug delivery systems. The development of chitosan-based nanoparticles has also contributed to the significance of chitin as a drug delivery system that can deliver drugs topically. Furthermore, chitin can be used in cancer treatment as a vehicle for delivering cancer drugs to a specific site and has an antiproliferative effect by reducing the viability of cells. Finally, chitosan can be used as a wound dressing in order to promote the faster regeneration of skin epithelial cells and collagen production by fibroblasts.

chitin

chitosan

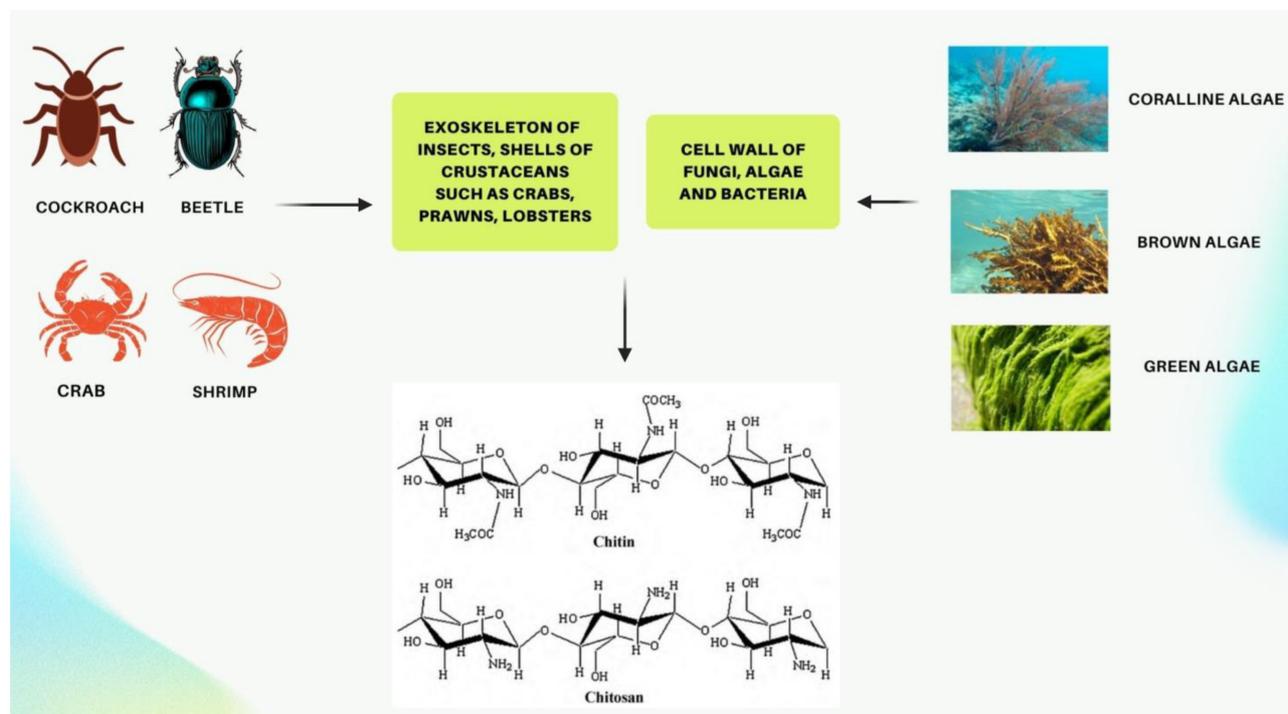
wound healing

drug delivery

## 1. Introduction

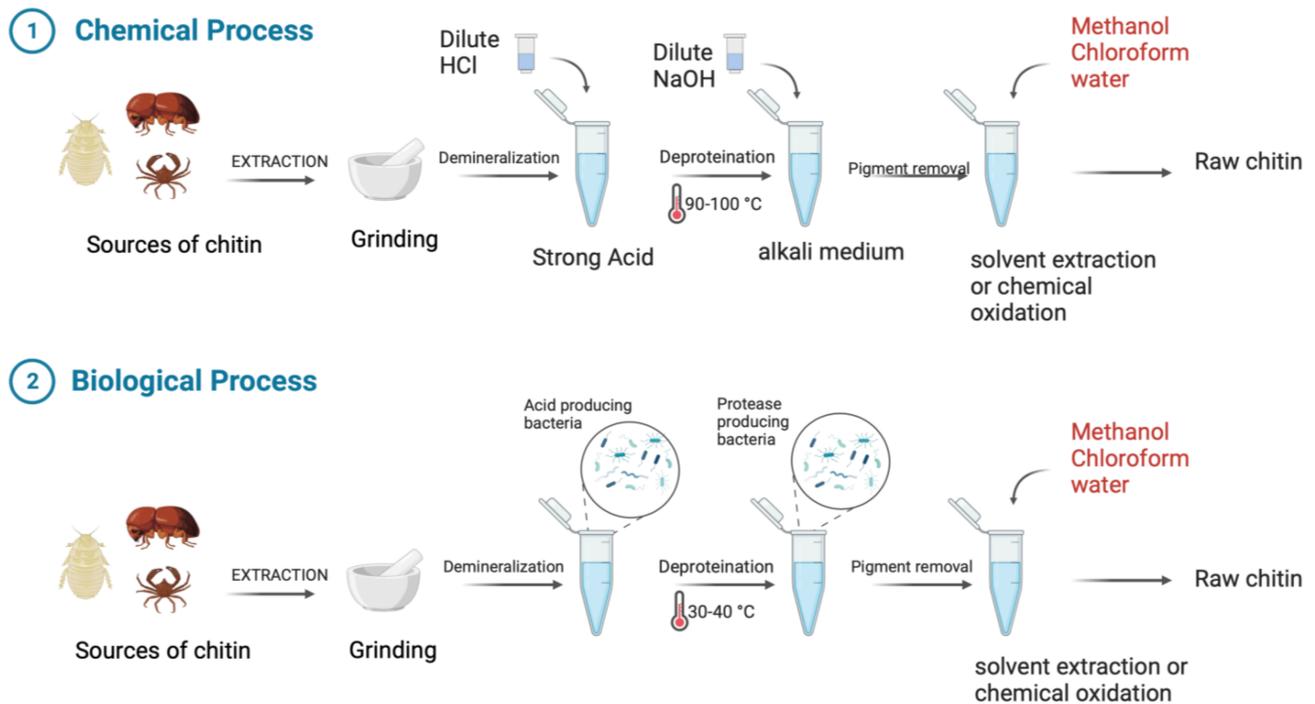
Chitin is a polysaccharide composed of crystallized N-Acetyl D-glucosamine monomers and 1–4 glycosidic bonds [1][2]. This structural polymer is highly abundant in the shells of marine crustaceans, cell walls of various organisms such as fungi, coralline algae, green and brown algae, and bacteria, as well as the exoskeleton of crustaceans, molluscs, and insects (Figure 1) [3][4][5][6][7][8][9]. In 2014, the first evidence of chitin inside the cell walls of the coralline algae *Clathromorphum compactum* was observed, and chitin was found to play an important role in the calcification process of this marine species [4]. Initially named fungine in 1811, it was subsequently renamed chitin in 1823 [10]. It occurs in about 19 animal phyla, bacteria, algae, and fungi, with a production rate of  $10^{11}$ – $10^{14}$  tons per year [10]. Although chitin is present in nature, multiple tons of it transform into marine shell wastes or other types of industrial wastes [11]. Chitin has recently gained much attention from scientists due to its important properties, which include nontoxicity, biocompatibility, and biodegradability, the ability to degrade by enzymes, enabling it to be used in many biomedical applications, including drug delivery, tissues engineering, wound healing, and cancer therapy. [11]. In spite of being the second most abundant polymer after cellulose, chitin is still largely unutilized because its semi-crystalline structure with a large number of intermolecular hydrogen bonds causes it to be insoluble in most solvents [6][12]. With the advent of new technologies, however, the partial N-deacetylation of chitin can now be converted into a soluble substance called chitosan. The deacetylation of extracted chitin is largely carried out in strong alkaline media, resulting in chitosan becoming soluble in acidic environments [13]. Hence, chitosan is a synthetically deacetylated form of chitin that can be used in the food industry as an edible and

biodegradable film for packaging food, food preservations, pharmaceuticals, water and wastewater treatment, cosmetics, wound dressings, and many other applications [1][6][11][14][15].



**Figure 1.** Sources of chitin and the structure of chitin and chitosan. [Created with [BioRender.com](https://www.biorender.com) accessed on 10 May 2022].

As mentioned earlier, the shells of crustaceans and shrimps, insect exoskeletons, and the cell walls of fungi such as *Aspergillus* and *Mucor* are the main sources of chitin and chitosan [16]. A large scale of industrial chitin production is derived from crab shells and shrimp shells, so recycling these wastes will yield valuable byproducts that can be used in medical and pharmaceutical applications [16]. To prepare chitin, the first step is to extract it from shellfish wastes. Shellfish wastes contain chitin, lipids, inorganic salts, and proteins as major components. Hence, chitin is extracted from these structural components using two common methods: chemical and biological processes (Figure 2) [17][18][19]. The purpose of these processes is to isolate chitin from minerals such as calcium carbonate and calcium phosphate and proteins and lipids or other macromolecules embedded in shells and cell walls [17]. In strong alkaline (>1 M NaOH) and acetic (>3 M HCl) environments combined with heat, chitin can be transformed into its deacetylated form, chitosan, or even partially fragmented [20]. Therefore, sulfuric acid, nitric acid, formic acid, acetic acid, and in particular, dilute hydrochloric acid are commonly used in the demineralization process of chitin [17][18][21]. The separation of proteins and pigments such as carotenoids is performed using dilute sodium hydroxide and acetone (or other organic solvents), respectively [17][18]. As an alternative method, biological processes may provide more desirable results due to their relatively low cost and environmental friendliness, low energy consumption, and reproducibility. They can also produce chitin with a higher molecular weight and better crystal structure [17]. Biological processes rely largely on enzymatic reactions and microbial fermentation [17][22]. However, the basis of these reactions, such as with the chemical process, is the production of acidic and alkaline products but from microorganism fermentation and enzymatic metabolites [17].



**Figure 2.** Chemical and biological processes to isolate chitin from animal sources. [Created with [BioRender.com](https://www.biorender.com) accessed on 10 May 2022].

Though chemical processes make chitin extraction easier and more efficient, they have some drawbacks when used on an industrial scale with industrial protocols. There are two main concerns about conventional methods of chitin extraction: the use of strong chemicals such as HCl, and the lower quality of raw extracted chitin due to contamination [15]. Therefore, obtaining high-quality chitin involves sophisticated instrumentation such as the use of ultrafiltration and molecular sieving. However, these techniques are costly, which creates significant financial barriers, especially for developing countries. Recent efforts are underway to develop novel methods for chitin extraction. As an example, Tissera et al. introduced a new process called “pretreatment” for the extraction of chitin from blue swimmer crab shell waste, proposing that this procedure helped improve the quality of extracted chitin for large-scale production [15]. They soaked crushed crab shell pieces in acetic acid (with concentrations of 0.05, 0.10, and 0.50 M) and citric acid with concentrations of 0.05, 0.10, and 0.50 M and found that acetic acid at 0.5 M resulted in the better cleaning of crab shells. They found that this pre-acid treatment helped the rigid structure of shells to become more flexible as well as slightly beginning the process of demineralization [15]. The results showed that this treatment with 0.5 M acetic acid helped remove any remaining muscle tissue that remained, which led to a lower concentration of NaOH being required for the deproteinization of crab shells. Furthermore, this pretreatment led to a lower concentration of acid required for the demineralization step since acetic acid aids in calcium carbonate removal [15].

Traditional chitin extraction methods have been thought of as time-consuming and expensive, with production times greater than one day. Therefore, other methods aimed at speeding up the process of chitin extraction have been studied in recent years. Kaya et al. proposed to treat the shells of crustaceans such as crabs, crayfish, and shrimp with two NaClO treatments (10 min each) before the main processes of demineralization and

deproteinization to ensure the complete disintegration and removal of pigments [23]. They found that by introducing NaClO, they were able to extract chitin in a shorter amount of time while the yield of chitin was similar to conventional extraction, and the color of extracted chitin was white, as in commercially available chitin [23]. The elemental analysis, FT-IR, and XRD of extracted chitin suggested that it has a high similarity to commercial chitin; consequently, they suggested that this new treatment of chitin should be considered for extracting chitin from crab shells, crayfish shells, and shrimp shells [23].

In another innovative study, Machałowski et al. isolated chitin from *Caribena versicolor* spider molt cuticles [24]. Arachnoids have a mineral-free cuticle, so demineralization (such as decalcification) can be skipped, and chitin isolation can begin with deproteinization and depigmentation [24]. Their study included removing pigments as well as chitin from spider cuticles using microwave-assisted methods (MWI) [24]. In the first step, which involved removing lipids and waxes from the cuticle, the cuticles were exposed to microwave radiation while being treated with chloroform and ethanol in a ratio of 2 to 1 [24]. In the second step, they used microwave radiation alongside NaOH treatment to remove other proteins and pigments from the cuticle [24]. The final step was to treat the cuticles with H<sub>2</sub>O<sub>2</sub> under microwave radiation in order to remove any residual pigments and obtain tubular chitin [24]. The bodies of *C. versicolor* spiders are covered with a strong exoskeleton (cuticle) consisting of an inner layer with chitin and proteins and an outer layer (without chitin) [24]. Due to this, these spiders lose a large number of chitin-rich cuticles during their molting cycle; therefore, tubular chitin from their cuticles could be used as a scaffold-based catalyst and tissue engineering material [24].

## 2. Chitosan as a Possible Drug Delivery Agent

The term “drug delivery systems” (DDS) refers to products that combine an active pharmaceutical agent with a suitable carrier—typically a polymer—and have been used in the pharmaceutical industry to improve the therapeutic potential and bioavailability of drugs [1][25]. By using hydrogels, scaffolds, micro- and nano-particles, and organic or inorganic matrices as carriers of active drug agents, this system delivers drugs in a sustained and controlled manner [1][10]. Among these, hydrogels, due to their chemical stability, are able to protect and maintain the encapsulated drug in extreme environmental conditions, and by dissolving in body fluids, lead to the release of the drug at the desired site and with the required concentration [1]. Controlled delivery is a basic property of the ideal DDS, which is used to maintain the plasma concentration of the active drug at a constant rate and within the therapeutic window [25]. Another important feature of DDS is targeted drug delivery or directing the active substance to a specific site [25]. In DDS, different types of vehicles such as tablets, capsules, and hydrogels are commonly used, depending on the target site and the route of administration [1]. The delivery of drugs can be performed either through invasive or non-invasive routes, such as parenteral and mucosal administration, respectively [25]. Mucosal drug delivery includes oral, buccal, nasal, pulmonary, and rectal routes, and most DDS use this route of administration to enhance mucoadhesiveness and, consequently, increase drug release [25].

A number of studies have been conducted on chitin and chitosan to determine their potential as drug delivery agents. Chitosan, for example, is significantly utilized in the production of hydrogels for drug delivery due to its valuable properties, including bioadhesion, having a polycationic surface that facilitates the creation of hydrogenic

and ionic bonds, and biocompatibility, meaning that in contact with living tissue or body fluids, it does not produce any toxins or elicit an immune response [1][2].

Marine sponges provide a good source of naturally occurring chitin that can be used for drug delivery by extracting chitin from their skeletons [26]. Kovalchuk et al. examined the potential application of fabric-like chitin scaffolds from the demosponge *Ianthella flabelliformis* for the first time [26]. The researchers found that these chitin scaffolds possess three-dimensional (3D) matrices that retain antiseptic decamethoxine absorbed from a 0.1% ethanol solution [26]. Moreover, they demonstrated that decamethoxine diffused from these mesh-like scaffolds into an agar diffusion assay and inhibited the growth of *Staphylococcus aureus*, confirming the potential use of pure chitinous scaffolds in drug delivery [26]. In another study, Zheng et al. prepared 10–100 µm carboxymethyl chitin microspheres (CMCH-Ms) and then encapsulated them in thermosensitive hydroxypropyl chitin hydrogels (HPCH) [27]. To maintain the spherical structure of microspheres with porous microstructures, they used physical cross-linking procedures and increased the temperature in an aqueous two-phase system without using cross-linking agents. Using the physical cross-linking method, carboxymethyl chitins are able to form microspheres at high temperatures because of their high acetylation levels, which make them temperature sensitive [27]. Similarly, hydroxypropyl chitin (HPCH) is also temperature sensitive, and it is capable of reversibly converting into solid hydrogels at elevated temperatures, enabling the in situ formation of hydrogels [27]. Two drugs, naproxen (NPX) and ropivacaine (Ropivacaine), were analyzed in vitro for their loading and release capacities into CMCH-Ms and HPCH gel scaffolds [27]. They found that CMCH-Ms/HPCH gel scaffolds sustained in vitro drug release over a longer period and caused fewer bursts of drug release. Therefore, they determined that drug-loaded CMCH-Ms/HPCH gel scaffolds could be used as a means of delivering local drugs [27].

Another technology that has attracted attention in recent years in the drug delivery industry is the use of nanomaterials, which include objects with a size of 1–100 nm [2][28]. Due to the size of these particles, they have a special feature as they follow the rules of quantum mechanics [28]. Nanotechnology can be used for accurate and precise imaging and drug delivery [2][29]. One method of drug delivery is the use of chitosan-based nanoparticles, which are used greatly in the mucosal route to transport the drug to the brain and eyes, as well as to treat diseases such as cancer and gastrointestinal and pulmonary diseases [29][30]. The solubility, diffusion, and size of chitosan-based nanoparticles determine the rate of drug release [31]. Most chitosan-based nanoparticles have a size between 100 and 400 nanometers. Photon correlation spectroscopy can be used to determine the size of the nanoparticles by measuring their Brownian motion [31]. Chitosan nanoparticles are stabilized based on several physical and chemical factors, including agglomeration, coagulation, temperature, the molecular weight of the polymer, and the pH of the medium [31].

In many eye diseases, drugs are used superficially on the ocular surface. However, due to defense mechanisms, less than 5% of drugs used topically are able to cross the cornea and reach intraocular tissue [32][33]. As a result, chitosan-based nanoparticles could be considered a possible solution to increase bioavailability and prolong drug bioavailability in the ocular tissue [32][33][34]. In a study by Silva et al., using nanotechnology, eye drops containing polymer-based nanoparticles consisting of the antibiotic ceftazidime were used to treat ocular infection with *Pseudomonas aeruginosa*, and the degree of mucoadhesion or the interaction between nanoparticles delivered

through the eye and ocular mucosal tissue was later analyzed [32]. The results of their study demonstrated that the use of polymeric-based nanoparticles facilitated the transport of antibiotics through the mucosal barrier of the eye as it enhanced the bioavailability of the drug and protected against degradation [32]. In addition, they were able to show that chitosan, due to its structural properties, increases the contact time between antibiotics and ocular mucosal tissue, so that a strong electrostatic interaction between the amine group of chitosan and salicylic acid, which is a main component of mucin, causes the drug to stay inside the eye longer. Other properties of chitosan have demonstrated its potential for drug delivery systems, including hydrophilicity, biodegradability, and antimicrobial activity [32].

In an innovative study, Cánepa et al. investigated the efficacy of interferon-alpha (IFN $\alpha$ ) delivery using chitosan-based nanoparticles through oral administration [35]. It has been known that the use of drugs via the oral route could reduce the absorption of drugs into the gastrointestinal tract due to the degradation by brush border enzymes and hepatic metabolism [35][36][37]. As a result, many pharmaceutical companies are trying to increase the bioavailability of prescribed orally-administered drugs [37]. IFN $\alpha$  is used as a drug to treat cancer and viral infections; however, due to its short half-life, it usually needs to be taken regularly by patients, and this regime could have its own side effects and drawbacks [38][39][40][41][42]. Cánepa et al. showed that the antiviral effect of encapsulated IFN $\alpha$  by chitosan-based nanoparticles was comparable to commercial IFN $\alpha$  on the market [35]. Furthermore, the bioavailability of the drug improved within the gastrointestinal tract due to the electrostatic interaction between the chemical groups in chitosan and salicylic acid in mucin, which led to the increased size of nanoparticles following the adsorption of mucin, as well as decreased surface charge of nanoparticles [35].

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