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Mini Review

Current Applications of Chitosan and Chito-Oligosaccharides. A Review

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Abstract

This review is focused on the chemical characteristics of chitosan and chito-oligosacharides as well as in their potential applications in different fields. We analyzed the origin and structure properties of these molecules and mentioned physicochemical parameters. The review deals mainly with the field of antifungal activity, therapy and nanotechnology in pharmaceutical; likewise, some factor that could explain the mode of action of these molecules used in these applications was proposed.

INTRODUCTION

The search for new biomolecules that are useful for human health and friendly to the environment has led to the study of molecules derived from plants, animals and microorganisms. Chitosan (CH) and chito-oligosaccharides (CHOS) are two biopolymers derived from chitin present in arthropods, fungi and bacteria. Shrimps and crab shells, obtained as byproducts of the food-processing industry, represent the main source of chitin. Chitin in a natural form is an insoluble polymer and differs in the way of forming the biological complexes characteristic to the organisms that contain it. In arthropods, chitin is covalently linked to proteins and tanned by quinones, in fungi it is covalently linked to glucans, while in bacteria chitin is diversely combined according to Gram (+/-) classification. The chemical structure of Chitin is defined as a linear polysaccharide consisting of β (1→4) linked to N-acetyl-D-glucosamine (GlcNAc). Chitin is insoluble in water and exists mainly in two crystalline polymorphic forms, α and β. α-Chitin is made of sheets of tightly packed alternating parallel and antiparallel chains and is found in the exoskeleton of arthropods, in insects, fungi and yeast cell walls. In β-chitin the chains are arranged in parallel. β-chitin occurs less frequently in nature than α-chitin, and can be extracted from squid pens. Chitosan is obtained through the deacetylation of chitin, and chito-oligosaccharide (CHOS) can be produced using chitin or chitosan as a starting material, using enzymatic conversions, chemical methods or combinations of them. Both are polymers with low toxicity, excellent biocompatibility and biodegradability. These characteristics make these molecules attractive to be used in many fields of human interest as pharmacy agriculture, food industry and health. In this review, we comment on some of the applications of chitosan and chito-oligosaccharides.

Chitosan

Definition and general properties: Chitosan is a modified, nontoxic carbohydrate polymer derived from chitin through enzymatic or chemical deacetylation [1]. It is formed by β-(1, 4) glucosamine units as its main component (> 80%) and N-acetyl glucosamine (< 20%) distributed randomly along the chain, forming a very complex chemical web [2] (Figure 1). It has a molecular weight average between 50 and 150 KDa, with a pKa value of 6.3 and is soluble in dilute acid solutions [3]. At this pH, chitosan behaves as a large polycationic molecule due to its reactive amino groups, which make its use in industry and research in a variety of fields possible [4].

Chitosan application: The versatility and ability of chitosan to form a polymeric complex base, in addition to the reactivity of its functional groups, make it an ideal substance for bioactive material fabrication [5]. In recent years, the use of CH in nanoparticles manufacturing, with different purposes has had significant development due to its biodegradability, biocompatibility and structure [6-8]. Several methods for the fabrication of chitosan nanoparticles have been described. For example Hosseini *et al.* (2014), proposed a two-step protocol for oregano essential oil encapsulation in a chitosan matrix; first, through hydrophilic emulsification and then through gelification in a chitosan-sodium tripolyphosphate mix. The analysis with FT-IR spectroscopy, UV-vis spectrophotometry, thermogravimetric analysis (TGA) and X-ray diffraction (XRD), (Figure 1) confirmed the production of regular and stable chitosan nanoparticles with size of 40-80 nm and 21-47% of encapsulation efficiency [9]. On the other hand, Unsoy et al. (2014), reported the development of pH-dependent chitosan coated magnetic nanoparticles for the release of antitumor drugs by an *in situ* method. This methodology

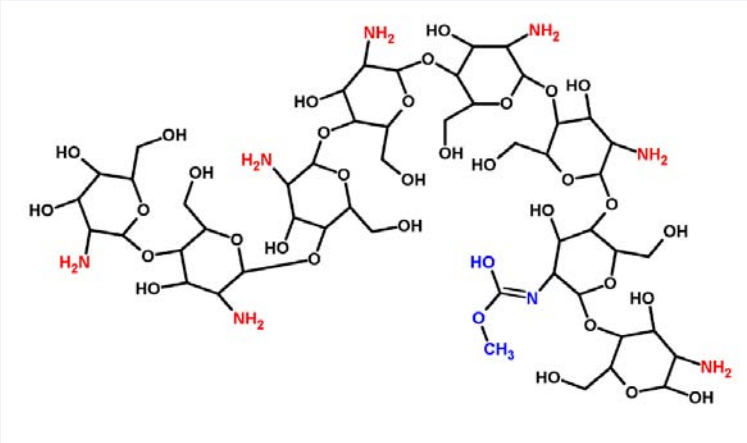

Figure 1 Chitosan structure. The interaction between reactive radicals allows the formation of a complex construction in the polymer matrix. Glucosamine amino group (red) and acetamide groups (blue) from n-acetyl glucosamine are highlighted.

consisted in the co-nucleation of Fe (II) and Fe (III) precipitated salts in the presence of chitosan-tripolyphosphate molecules optimized with the addition of NH_4OH. The diameters of nanoparticles were found to be 103 nm, 86 nm, 66 nm and 58 nm and were tried in the release of Doxorubicin to treat MCF-7 breast cancer. The study observed that the optimal condition for release of anti-cancer drug was at pH 4.2 while the nanoparticles are quite stable at pH 7.4 [10]. The release of pharmaceutical compounds such as insulin, hormones, controlled drugs, antioxidants as well as vitamins, food supplements and vaccines have been studied in a chitosan modified nanoparticles matrix [11-15], where the use of chitosan improves the stability and environment interactions enhance the therapeutic effects. Also, the use of chitosan nanoparticles has been proved to be an antimicrobial agent vs different bacterial and fungi agents [16,17]. For example, Shrestha et al. (2014), observed the antibacterial behavior of bioactive polymeric chitosan nanoparticles functionalized with rose-bengal against *Enterococcus faecalis* by altering the biofilm stability of dental infectious agent. This study observed that chitosan nanoparticles stabilized dentin-collagen structure integrity by a process of photo-cross-linking [18]. Also, Zain et al. (2014), investigated uni and bimetallic silver-cupper chitosan nanoparticles as agent against *Bacillus subtilis* and *Escherichia coli* to establish the best system for the application of these green nanoparticles. The researchers observed that the highest antibacterial activity was obtained with bimetallic Ag/Cu nanoparticles with minimum inhibitory concentrations (MIC) of 0.054 and 0.076 mg/L against *B. subtilis* and *E. coli*, respectively [19]. Exists others nanoparticles that were showed an effective inhibitory effect in the growth of several microorganisms such *Staphylococcus aureus*, *Listeria monocytogenes*, *Salmonella enteritidis, Candida albicans*, *Candida nonalbicans* and *Candida tropicalis* [20,21]. The mechanism of the antimicrobial effect of chitosan is not fully clear and is associated with the degradation of cellular structures, interference with metabolism, damage in biomolecules, modification in cell permeability, as well as activating some up-regulation mechanisms in the pathogen and/or host [22-25]. Another important use of chitosan nanoparticles is in cancer treatment, either as a specific drug liberator or as a therapeutic agent [26,27]. It was demonstrated that chitosan nanoparticles are capable of interfering with the development of tumor cells in different levels; for example, through the interaction with specific membrane receptors to diagnostic or therapeutic strategies [28]; the liberation of chemo and radio specific drugs in target cells [27]; the inclusion of siRNA for the tumor growth inhibition [26]; or a mix of a variety of strategies [29,30].

Although the development and characterization of chitosan nanoparticles has been a widely explored field in recent years, the original polymer also has a variety of applications. In this context, as a consequence of its ability to generate complex with metal ions, chitosan is useful in the decontamination of industrial wastewater [1]. In addition, its polycationic character confers flocculating action [31], which was also was as support in the enzymes and cells immobilization process for biotechnology and the food industry [32,33]. Chitosan is also an excellent agent for forming fibers, films and membranes [34-36] and can be prepared in the form of microspheres, microcapsules and bio gels for the cosmetic and pharmaceutical industries [37,38]. As a therapeutic agent chitosan was tested for reduction of cholesterol levels, as a stimulant of the immune system, as an agent to reduce corporal weight and alternative therapy in burns [39-41]. Its antimicrobial capacity against pathogens and microorganisms that damage human health as well as animals, fruits and vegetables, has also been described [22,42,43].

Chitosan has an important role in plant systems owing to its interaction with the protection and detoxification mechanisms, as well as gene expression. Because of this, chitosan has potentially important applications in agricultural biotechnology [44]. In other research, a postharvest chitosan treatments mixed with different organic and inorganic acids were proved to improve the effectiveness in controlling postharvest diseases of strawberries. Chitosan formulation showed an effective behavior against gray mold and *Rhizopus* rot in strawberries compared with others protection systems such as benzothiadiazole, calcium and organic acids [45]. On the other hand, chitosan was tasted against the maize phytopathogenic agent *Ustilagomaydis*, an important

fungi model. This showed that low molecular weight chitosan with an 80% deacetylation degree was able to completely inhibit the growth of corn smut in a concentration of 1mg/mL in 12 h destroying the fungi´s cellular membrane [22]. This effect could be an opportunity to implement systems based on chitosan for the control of different smut fungi to prevent cereals plant infection and avoid crop losses that represent significant economic losses.

Even though chitosan has a wide and numerous applications, it still is a polymer with limitations, the most important being related with its insolubility at neutral pH and high viscosity [46-48]. As response of these disadvantages, chitosan-based compounds have been developed, which allows to use this polymer at pH 7.0, and these are chito-oligosaccharides. Other compounds modified by the addition of positively or negatively charged groups have also been developed, but they will not be addressed in this review.

Chito-oligosaccharides

Definition and general properties: Chito-oligosaccharides (CHOS) are low molecular weight derivatives from chemical or enzymatic hydrolysis of chitosan. CHOS are formed mainly by units of glucosamine, from 2 to 7 repetition joined by β (1-4) bonds (Figure 2) [46]. Their low molecular weight, in addition to their higher degree of deacetylation (DD), favor their reactivity and improve the water solubility [49].

CHOS are short lineal chains with the same structure as chitosan, and most are not able to create complex matrixes like the original polymer. However, the characteristics of CHOS allows them to interact in different levels with the environment, making them attractive molecules and in some cases with more powerful effects than chitosan, especially when used as therapeutic and antimicrobiological agents [50,51] (Figure 2).

CHOS application: CHOS can be used in a wide variety of biotechnological areas, especially in medicine and pharmacy, due to the beneficial effects on human health. From this point of view, it was observed that CHOS are able to potentiate and modulate the immune system of eukaryotic models [52,53]. Lin *et al*. (2012), demonstrated that a diet supplemented with CHOS is able to protect against *Vibrio harveyi* infection in *Trachinotus ovatus. In their analysis they demonstrated significant differences, in immunological parameters such as* total leukocyte counts, differential leukocyte counts, respiratory burst activity, lysozyme and superoxide dismutase (SOD) activity when the levels of dietary CHOS were increased, at level of 4.0 g kg^{-1} CHOS [54]. In the same context, CHOS showed an immunity-enhancing. In the murine model, it compared the antibody response of BALB/c mice inoculated with vaccine and CHOS for 3 weeks that were then infected with deadly flu virus A/PR/8/34 (H1N1). The results indicated that using CHOS as an adjuvant increased the antibody content in serum remarkably and increased the antiviral defense in the mice, enhancing the immune reaction to the vaccine [55]. The exact mechanism of this cellular behavior by the presence of CHOS has not been fully explained; however, this effect was associated with the activation of transcriptional factors into the cell through the interaction with CHOS as well as the immune cells differentiation as a consequence of the CHOS's similarity to bacterial LPS, among others [56,57].

Used as anticancer compounds, CHOS showed their effectiveness in reducing the development of cancer cell models, tumor growth, the metastatic potential of gastric cancer and promote radio sensitivity in colon cancer, among many other reported activities [58-61]. In another context, CHOS were used as metabolism modulators to prevent a variety of metabolic disorders. It was observed that CHOS were able to increase the plasma concentration of high density lipoprotein-cholesterol (HDLC) and, therefore, decreased the potential risks of cardiovascular diseases [62] as well as reduce the total cholesterol levels [63]. They also reduced the triglycerides accumulation in hepatic cells through the regulation of genes

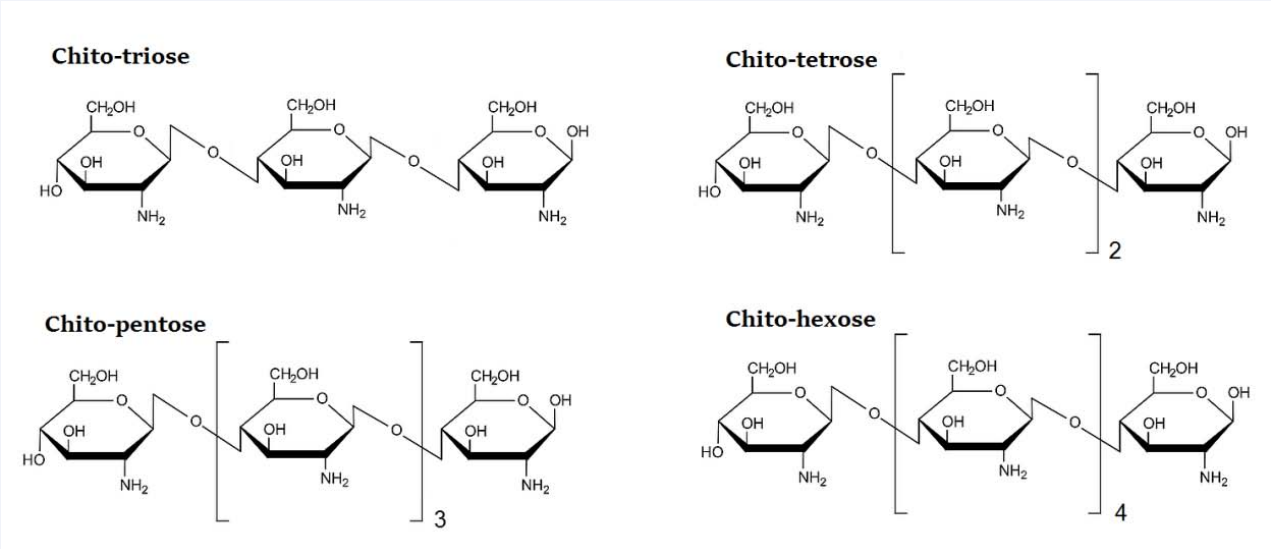

Figure 2 Some chito-oligosaccharides structure. The main component of CHOS is glucosamine connected by β (1-4) glycosidic bonds. CHOS usually has a higher deacetylation degree due to their conformation.

involved in the synthesis and degradation of this kind of molecules [64]. In addition, CHOS increased the mitochondrial biogenesis in rat model, suggesting that they are able to be used as a food supplement to increase exercise endurance or for treatment of energy disorders [65]. Moreover, CHOS plays an important role in the prevention of Alzheimer's disease by protecting neuronal cells from death, suppressing hyperphosphorylation of *tau* protein, involved in Alzheimer´s disease, reducing the activity of β-secretase, antioxidation, chelating copper ions, and suppressing the activity of acetyl cholinesterase [66]. Although CHOS have demonstrated benefits in human health and were considered an attractive alternative for treatment in a large number of disorders, it is important consider the secondary effects by the ingestion of CHOS. It was observed that these molecules could affect the normal function of kidney as if they were aminoglycoside antibiotic [67], therefore it is important to do a deep analysis in the use of CHOS as a therapeutic agent and considers the risks involved in its use.

On the other hand, CHOS were tested as antimicrobial agents vs several pathogen and no pathogen bacteria and fungi. It was observed that CHOS had high antibacterial activity against *Bacillus subtilis*, *Staphylococcus aureus*, and *Escherichia coli* when they are in a concentration of 100 mg/mL [68]. Also, CHOS showed stronger antimicrobial activity against *Bacillus cereus, Staphylococcus aureus, Serratia liquefaciens* and *Lactobacillus plantarum* when they are part of a semi synthetic protective film [69]. It was demonstrated that CHOS with different degree of polymerization were able to inhibit the growth and spore germination of *Botrytriscinerea* and *Mucorpiriformis*, as well as inhibited the growth of the phytopathogenic agent *Ustilagomaydis* [22,70]. The mechanism of inhibitory effects by CHOS against bacteria and fungi is related with their size, DD of CHOS and reactivity of their functional groups, this by the alteration of internal systems as well as their interaction with different morphological and physiological areas of the microorganisms [22,68]. However, a simple rule for the mode of action of CHOS as antimicrobial compounds cannot be generated in order to explain the effects of these molecules. The final results depend on the internal characteristics of the model and the possible interaction between it and CHOS, which opens an opportunity to extend the knowledge on the use of CHOS as an antimicrobial tool.

CONCLUSION AND PERSPECTIVES

In spite of the information mentioned in more recent reviews about chitosan or chito-oligosaccharides, there still is scarce informationunderlying the bioactivity of these biomolecules. Understanding the mechanisms on the mode of action of CH and CHOS will bring more and acute information, because by now all the information produced has been realized with heterogeneous mixtures. Another aspect not mentioned in the studies is the potential environmental impact of the use of these biomolecules applied in most the human activities, going from agriculture to human health and nanotechnology. We need to go so far in depth knowledge in the mode of action and bioactivities of those molecules. As an antifungal, it is necessary to try more microorganisms; for therapeutic use, we need to ensure the absence of undesirable or collateral reactions; whereas for the environmental impact, it is important to consider the time for degradation.

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