Chitosan is an innate cationic biological polysaccharide polymer, naturally obtained from chitin deacetylation, that possesses broad-spectrum properties such as antibacterial, biodegradability, biocompatibility, non-toxic, non-immunogenicity, and so on. Chitosan can be easily modified owing to its molecular chain that contains abundant active amino and hydroxyl groups, through various modifications. Not only does it possess excellent properties but it also greatly accelerates its solubility and endows it with additional special properties. It can be developed into bioactive materials with innovative properties, functions, and multiple uses, especially in the biomedical fields. In this paper, the unique properties and the relationship between the molecular structure of chitosan and its derivatives are emphasized, an overview of various excellent biomedical properties of chitosan and its current progress in the pharmaceutical and nutraceutical field have prospected, to provide the theoretical basis for better development and utilization of new biomedical materials of chitosan and its derivatives.

1. Definition

Chitosan is an innate cationic biological polysaccharide polymer, naturally obtained from chitin deacetylation, that possesses broad-spectrum properties such as antibacterial, biodegradability, biocompatibility, non-toxic, non-immunogenicity, and so on. Chitosan can be easily modified owing to its molecular chain that contains abundant active amino and hydroxyl groups, through various modifications.

2. Introduction and history

Only by tracing back the history, we can look forward to the future. In 1811, chitin was first discovered in mushrooms and named fungi by French scholar Brano [1]. Chitin is the second largest natural biopolymer only after cellulose and exists extensively in marine organisms (Figure 1), such as the shells of shrimp and crab, bacterial and algal cell membranes, shells and skeletons of mollusks and cell walls of higher plants. It is a recyclable, renewable and inexhaustible resource, mainly distributed in coastal areas [2]. It is reported that there are about 10 billion tons of chitin biosynthesis each year, more than 150,000 tons of chitin are available for commercial purposes [3]. Chitin constitutes a major component of arthropod exoskeletons, tendons and the linings of their excretory, respiratory and digestive systems. It is also found in the eye iridophores and epidermis of cephalopods and molluscan arthropods and the cuticle of vertebrates [4], up to now, its commercial sources are mainly crabs, shrimp, krill shells, fungi, etc. The crustacean shell is composed of 30-40% protein, 30-50% calcium carbonate and calcium phosphate and 20-30% chitin. The ratio of chitin obtained from dried shrimp and crab processing waste was 14-27% and 13-15% respectively [5]. Due to the intractable molecular structure of chitin, it is still the main underutilized resource despite its easy availability and huge annual output. It has vital research significance as a biomaterial with potential activity in different fields.

Figure 1. Overview of production and structure of chitosan.

In 1894, the German scientist Hopper Seyler [6] used potassium hydroxide solution to boil chitin for modification and obtained deacetylated chitin, which was named chitosan. Chitosan is a high molecular weight compound with a deacetylation degree higher than 55% of chitin, the deacetylation degree or degree of acetylation (DA) is derived from the amount of the acetamido-2-deoxy-d-glucopyranose monomeric unit that exists in the polymer chain. The deacetylated chitin (chitosan) is the only natural basic polysaccharide, soluble in aqueous solutions of inorganic or organic acids, with more than 90% glucosamine content, which is found in large quantities in the biological world.
Chitosan and its derivatives are also widely used in tissue engineering, especially as biological scaffolds of skin and bone, due to its ability to promote wound healing, unique bactericidal and biodegradable properties and providing certain nutrients for cell growth. In the process of wound healing, chitosan can regulate the function of macrophages and the secretion of cytokines such as interleukin and tumor necrosis factor. Aments of studies have confirmed that the unique biomedical properties of chitosan and its derivatives are closely related to its structure. Chitosan and its derivatives act as wound healing materials with a broad application prospect, which is attributed to their advantages of promoting wound healing, unique bactericidal and biodegradable properties and providing certain nutrients for cell growth. In the process of wound healing, chitosan can regulate the function of macrophages and the secretion of cytokines such as interleukin and tumor necrosis factor. Aments of studies have confirmed that the unique biomedical properties of chitosan and its derivatives are closely related to its structure.

According to the Pharmacopoeia of the people’s Republic of China (Volume 4), chitosan is used for pharmaceutical excipients, disintegrants, thickeners, etc. Chitosan has a variety of biomedical properties and is widely used in wound dressings, orthopedics, dentistry, antitumor therapy, vascular repair and other fields. Aments of studies have confirmed that the unique biomedical properties of chitosan and its derivatives are closely related to its structure. Chitosan and its derivatives act as wound healing materials with a broad application prospect, which is attributed to their advantages of promoting wound healing, unique bactericidal and biodegradable properties and providing certain nutrients for cell growth. In the process of wound healing, chitosan can regulate the function of macrophages and the secretion of cytokines such as interleukin and tumor necrosis factor. Aments of studies have confirmed that the unique biomedical properties of chitosan and its derivatives are closely related to its structure.

### 3. Application of Chitosan Biomaterials

According to the Pharmacopoeia of the people’s Republic of China (Volume 4), chitosan is used for pharmaceutical excipients, disintegrants, thickeners, etc. Chitosan has a variety of biomedical properties and is widely used in wound dressings, orthopedics, dentistry, antitumor therapy, vascular repair and other fields. Aments of studies have confirmed that the unique biomedical properties of chitosan and its derivatives are closely related to its structure. Chitosan and its derivatives act as wound healing materials with a broad application prospect, which is attributed to their advantages of promoting wound healing, unique bactericidal and biodegradable properties and providing certain nutrients for cell growth. In the process of wound healing, chitosan can regulate the function of macrophages and the secretion of cytokines such as interleukin and tumor necrosis factor. Aments of studies have confirmed that the unique biomedical properties of chitosan and its derivatives are closely related to its structure.
ability of no expansion in water, high porosity and water absorption, interconnecting pores and uniform pore size, which are suitable for material exchange and growth metabolism of cells [94, 95, 96, 97, 98]. Chitosan scaffolds degrade without toxicity or inflammatory reactions eventually for the formation of the new tissue [99]. So, many porous chitosan scaffolds have been used for skin fibroblasts, keratinocytes and bone osteoblasts [100]. Yeh et al. [101] synthesized chitosan cellulose scaffolds, grafted with sodium tripolyphosphate and polymethyl methacrylate, and finally were coated with gelatin, Schwann cells and fibroblasts. Chitosan provides a growth scaffold for cells, adheres to cells on the surface and makes cells grow rapidly. Shaltoukia et al. [102] prepared porous nanocomposite scaffolds containing polycaprolactone and 45s bioactive glass nanoparticles with different nanoparticles (about 40 nm in diameter) by solvent casting technology. This material can play a good role in bone tissue engineering. Many kinds of chitosan composites such as thin film, gel, sponge and granule have been produced [103, 104]. Chitosan-based systems for soft tissues like skin, adipose tissue, cornea, liver, nerve, CNS and blood vessel reengineering have been reviewed [105, 106]. In skin tissue engineering, the rigid structure of chitosan fibers can enhance the mechanical resistance of the dermal matrix and prolong the degradation of the dermal matrix by wound cell collagenase [107]. In cartilage tissue engineering, chitosan sustained-release microspheres have good drug loading and drug-releasing properties. Microsphere scaffolds can well maintain the phenotype of chondrocytes, promote their adhesion and proliferation, and have a good application prospect in the construction of cartilage and repair of cartilage damage as a carrier of chondrocytes. Chitosan and its derivatives have been extensively applied in the study of artificial nerves because of their excellent biodegradability and biocompatibility. During the construction of artificial nerves, the function of normal peripheral nerves was not affected, which could promote nerve regeneration and provide conditions for the attachment, migration and proliferation of Schwann cells to play their normal functions.

Gels, nanoparticles, films, compressed tablets, beads and microspheres are currently used as potential drug delivery systems [108, 109, 110]. Chitosan has excellent biological activities as mentioned before and has been widely used in the study of the drug carrier systems as drug conjugates, hydrogel systems and biodegradable release systems [111, 112, 113]. It is mainly used in gene therapy, biological imaging, delivery of proteins/peptides, anti-inflammatory drugs, growth factors, antibiotics and vaccines. Drug delivery routes include oral administration, nose, eye and percutaneous administration [114, 115]. The ionic interaction between the negatively charged sialic acid substructure in the mucus and the positively charged primary amino group of chitosan polymer could offer adhesion and permeability properties of chitosan. Self-assembled nanospheres were prepared by chemically-linked active amino groups on the chitosan backbone, which can circulate in the blood for a long time without being engulfed and can be transplanted to the target ligand, which is easy to deposit in the designated lesion site for treatment. Kim [116] used carbodiimide to connect the bile acid to the glycolytic chitosan skeleton so that the chitosan had strong hydrophilicity, and the nano-microspheres circulated in the blood for a long time and could be loaded with doxorubicin, paclitaxel, doxycycline and other anticancer drugs to effectively treat tumors.

Chitosan can attach nucleic acids via electrostatic bonding and also could be used to create non-viral gene delivery vectors, which enter into the cells without alienation of the DNA-chitosan complex [117, 118, 119, 120]. It shows the main part in both lysosomal escape and membrane adhesion of the encapsulated DNA for effective cell transfection. Garcia et al. [121] prepared siRNA/folate poly-chitosan lactate nanoparticles by ionic gelation, showing the potential of effective gene therapy for ovarian cancer. Song [122] investigated the antitumor activities of chitosan with a molecular weight of 3 K, 65 K and 600 kda and the zero-valent selenium (Se⁰) nanoparticles stabilized by oligosaccharides. High molecular weight chitosan stabilized nanoparticles are easier to release selenium than low molecular weight chitosan, and to be absorbed by HepG2 cells through electrostatic action. Additionally, they are more effective in inhibiting the activity of HepG2 cells. These nanoparticles could produce highly toxic Se⁴⁺ from the less toxic Se⁶ and release selenium upon high ROS production by cancer cells. This high toxic Se⁴⁺ causes apoptosis and mitochondrial dysfunction via consuming antioxidant enzymes. Chitosan and its derivatives can regulate the immune system through molecular mediation, enhance the body’s resistance to various pathogenic microorganisms, and show antitumor activity. The antitumor activity of chitosan varies with the molecular weight and the substituted functional groups. Additionally, there are more negative charges on the surface of tumor cells, and chitosan and its derivatives are polycationic electrolytes, which are easy to adsorb to the surface of cancer cells and neutralize the charges, which can inhibit the growth and metastasis of tumor cells and even kill cancer cells.

In a word, the research and application of chitosan and its derivatives are the important direction of biomedical materials research in recent years, which deliver new materials for the development of biomedicine. At present, the research on chitosan is far more than the above-mentioned applications. With the continuous update of science and technology, chitosan and its derivatives in biological medicine are reported quite more every year, including anticancer, antiviral drugs, wound healing promoting materials, implants or blood components, substitutes of tissue components and applications in biotechnology as carriers of biological separators, fermentation industry, biomacromolecules and biosensors. This explains its importance in various fields, especially as biomedical materials. Although chitosan and its derivatives have a significant effect in biomedicine, due to the shortcomings of poor solubility and mechanical properties of chitosan, which limits the development of pure chitosan in the medical field. Additionally, there are still some key scientific problems to be solved, such as the uneven particle size, the deactivation of entrapped drugs, the inability to entrap hydrophobic drugs, and the difficult regulation of release. Therefore, the modification of chitosan, grafting with other materials and strengthening the development of drug loading system, design and construction of safe and efficient granules for protein-peptide sustained release, antitumor drug targeting, intraocular drug delivery and therapeutic vaccine adjuvant are the research hotspot of chitosan as biomedical materials.

4. Conclusions and Perspectives

Chitosan has good histocompatibility, biodegradability and excellent biomedical properties such as improving immune activity, antitumor, antibacterial, hemostasis and promoting wound healing. These properties are influenced by the degree of deacetylation, molecular weight and groups, especially amino groups of chitosan. To find out the relationship between these properties and its molecular structure has become the focus of many researchers, which provides a theoretical basis for the better development of new materials of chitosan and its derivatives, and makes it have a better application prospect in the field of biomedicine.
The research on the characteristics and application of chitosan in biomedicine has developed rapidly and become one of the hot research fields. Compared with α-chitosan, β-chitosan has weaker binding force, better solubility and biological activity. However, there are a few kinds of research on it at present. Therefore, exploring the economic and environmental protection of β-chitosan production process and modification research may become one of the research hotspots of potential biomedical materials in the future.

With the rapid development of biomaterials, higher requirements and challenges have been put forward for scaffold materials and drug carries. However, chitosan and its derivatives limit their application to some extent due to their defects, which need further study. At the same time, it is also necessary to strengthen the research of composite with other biomaterials to form new functional materials of marine organisms with multiple advantages, which should be one of the research hotspots of biomaterials in tissue engineering.

**Keywords**

chitosan;structure;modification;properties;pharmaceutical application

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