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Review

Advances in characterisation and biological activities of chitosan and chitosan oligosaccharides

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ABSTRACT

Chitosan and chitosan oligosaccharides (COS) have been reported to possess various biomedical properties, including antimicrobial activities, immuno-enhancing effects, and anti-tumour activities. COS have attracted considerable interest due to their physicochemical properties, and potential applications in the food and pharmaceutical industries, especially in cancer therapies. This paper describes the preparation of COS and their physicochemical properties, and modification, which aids understanding of their biological activities. Based on the latest reports, several biological and anti-tumour activities of COS will be discussed. The proposed anti-tumour mechanisms of COS are summarised, to provide comprehensive insights into research on the molecular level. Finally, the potential applications and future development of the biopolymer will be discussed.

Contents

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1. Introduction

Chitin is the most abundant polysaccharide in natural macromolecules, next to cellulose, as the major component of the shells of crustaceans, such as crabs and insects. Although chitin has many functional specialties in various areas, the low water solubility and poor biodegradation performance restricts its applications. As the degraded products of chitosan or chitin, chitosan oligosaccharides (COS) have recently been produced by several methods, such as enzymatic and acidic hydrolysis. The degraded products have a smaller molecular weight, and are readily soluble in aqueous solutions, making COS perform valuable biological activities at the cellular or molecular level. The study of COS has been increasing not only for the regeneration characteristics of abundant natural resources, but also for their biological compatibility and effectiveness. There are numerous reports on the biological activities of COS and their potential applications in food (Du, Wang, Yuan, Wei, & Hu, 2009), pharmaceutical (Berger, Reist, Mayer, Felt, & Gurny, 2004), agricultural, and environmental industries (Crini, 2005). As natural antioxidants (Xie, Xu, & Liu, 2001), COS possess multiple properties, such as anti-inflammatory, antimicrobial (Choi et al., 2001), hypocholesterolemic (Muzzarelli et al., 2006), immunostimulating (Feng, Zhao, & Yu, 2004), and anti-tumour activity (Salah et al., 2013). Moreover, the features of innately biocompatible, non-toxic, and non-allergenic to living tissues have made COS a promising drug carrier and tissue-engineering scaffold for nano-/micro-architecture (Dash, Chiellini, Ottenbrite, & Chiellini, 2011). This review summarises the preparation methods and modification of COS, discusses well-known biological activities of COS, and highlights the anti-tumour property and its relevant mechanisms. The future utilisation and potential development is also elucidated.

2. Characterisation of chitosan and COS

Chitosan is the *N*-deacetylated form of chitin and linear polysaccharides with a variable degree of *N*-acetylation, which is composed of less than 20% β-(1,4)-2-acetamido-D-glucopyranose and more than 80% β-(1,4)-2-amino-D-glucopyranose (Fig. 1A). Chitosan is water-insoluble and highly viscous in dilute acidic solutions. This solubility drawback may restrict the applications of chitosan in biological fields. In contrast, as the hydrolysed products of chitosan, COS have better solubility and lower viscosity under physiological conditions because of shorter chain lengths and free amino groups in D-glucosamine units (Fig. 1B). As moderately cationic polymers, COS have one amino group and two hydroxyl groups in repeated residues of glycoside (Agrawal, Strijkers, & Nicolay, 2010). These properties attracted a great amount of interest from an increasing number of researchers, who focus on the study of chitosan in the oligosaccharide form.

2.1. Preparation of COS

COS are the degraded products of chitosan or chitin. The second most abundant polysaccharide in nature following cellulose is chitin, which uses shell waste from shrimps, lobsters, krill, and crabs as main commercial sources. Degradation of the *O*-glycosidic linkages of chitosan by different methods, results in different numbers and sequences of glucosamine (GlcN) and GlcNAc units as well as different degrees of polymerisation (DP). Over the past few years, several technological approaches have been taken in preparing COS, including acid hydrolysis (Tsao et al., 2011), the enzymatic method (Wu, 2011), ultrasonic degradation (Liu, Bao, Du, Zhou, & Kennedy, 2006), and oxidative degradation (Xia, Wu, & Chen, 2013). The molecular weight decreased after the *O*-glycosidic bonds were broken by these methods.

Among the widely applied COS preparation methods, acid hydrolysis is more commonly used than the enzymatic method in the industrial production. Most of the acidic hydrolysis products have a low DP, mainly from monomer to tetramer in quantitative yield (Jeon, Shahidi, & Kim, 2000). However, chemical hydrolysis has several disadvantages in terms of popularisation, due to generation of detrimental by-products, a high risk of environmental pollution, and low production yields.

In this context, enzymatic production methods have drawn great interest with concerns of safety and toxicity. Enzymatic processes could minimise adverse chemical modifications and promote biological activities. Many nonspecific enzymes, such as cellulase (Lin, Lin, & Chen, 2009), as well as chitosanase (Song, Alnaeeli, & Park, 2014), have been used in the preparation of COS. It has been observed that chitosanase obtained from microbes gives relatively higher yields of COS compared to those derived from other sources. Although chitosanase obtained from microorganisms has excellent effects on COS production, the high cost restricts its use in large-scale industrial applications (Zhang, Du, Yu, Mistutomi, & Aiba, 1999). To reduce the production cost, reuse of hydrolytic enzymes is recommended.

Initially, enzymatic hydrolysis of COS was carried out in batch reactors (Izume & Ohtakar, 1987). The high cost of non-reusable enzymes, and low yields due to poor control of DP in a batch reactor system, stimulate new strategies to prepare COS. By contrast, the column reactor with immobilised enzymes has more technological advantages, including enzyme reusability, continuous operations, rapid termination of reactions, and well-controlled product quality (Song et al., 2014). However, this method is inefficient in

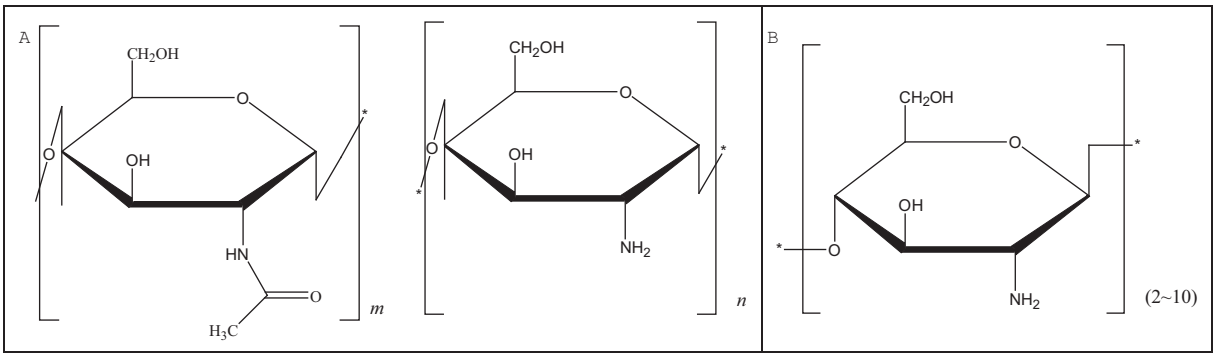

Fig. 1. The chemical structures of chitosan (A) and chitosan oligosaccharides (B).