



Review

Chitooligosaccharides and their biological activities: A comprehensive review

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ABSTRACT

Chitin is the most abundant natural polysaccharide and chitosan is its most important derivative. Regardless of having various bioactivities, the water insolubilities of chitin and chitosan limit their applications in many industries. The physical, chemical or enzymatic depolymerization of chitin and chitosan deliver chitooligosaccharides (COS): water-soluble and low molecular weight derivatives, superior to the parent polymers in multiple aspects. COS exhibit an enormously wide range of biological activities and a remarkable potential to be applied in various industries. This review has fully addressed the latest research on the biological activities of COS and the molecular mechanism behind these activities in a correlation with their physicochemical properties. Furthermore, an attempt has been made to report the commercially available COS products. The bioactivities discussed here may offer new understanding of the applications of COS in numerous sectors.

1. Introduction

1.1. Chitin

Chitin, a water-insoluble, cationic amino polysaccharide of β -1,4-linked N-acetylglucosamine (GlcNAc), is the most plenteous biomass after cellulose, and commonly found in crustacean shells, insect cuticles, and fungal cell wall (Heggset et al., 2010; Mahata et al., 2014). It was first isolated from a mushroom by Henry Braconnot in 1811 (Braconnot, 1811). Chitin has three polymorphic forms named as α , β , and γ chitin, which differ in their degree of hydration and size of the unit cell. The α and β chitin are composed of layers of polysaccharide chains arranged in an anti-parallel and parallel manner, respectively, while γ chitin contains parallel polysaccharide chains interspersed with anti-parallel single chains (Mekasha et al., 2017). Chitin is biodegradable and biocompatible, therefore, biomedical applications of chitin have been reported frequently (Park & Kim, 2010). Accordingly, chitin has numerous applications in food industry, agriculture, wastewater treatment, textile industry, microbiology, nanotechnology, chemistry,

material science, tissue engineering and drug delivery.

In crustacean shell wastes degradation of chitin is a time-consuming process, therefore, disposal of seafood processing discards has become an environmental distress and a challenge for all the shellfish producing countries (Arbia, Arbia, Adour, & Amrane, 2013). The best utilization of crustaceans shell waste is to convert it into valuable products such as chitin, thus, the main commercial sources of chitin are the crustacean shell wastes. The natural production of chitin in living organisms is estimated to 10^{11} tons per year (Elieh-Ali-Komi & Hamblin, 2016). Most of the chitin is used as raw material for the production of the glucosamine (GlcN), which is the number one dietary supplement in the USA, used for pain relief of osteoarthritis (Aam et al., 2010). One major limitation, which impedes its applications in living systems is the water insolubility. To cater this, chitin must further be converted into its derivatives, which are of utmost interest because of their applications in multiple fields.

Abbreviations: GlcN, glucosamine; GlcNAc, N-acetylglucosamine; FA, fraction of N-acetylated residues; DA, degree of N-acetylation; DP, degree of polymerization; MW, molecular weight; PD, molecular weight distribution; PA, pattern of N-acetylation; COS, chitooligosaccharides; NA-COS, N-acetyl chitooligosaccharides; DD, degree of deacetylation; HPLC, high performance liquid chromatography; HILIC, hydrophilic interaction liquid chromatography; UHPLC, ultra-high performance liquid chromatography; HPAEC-PAD, high performance anionic exchange chromatography with pulsed amperometric detection; CE, capillary electrophoresis; FT-IR, fourier transform infrared spectroscopy; NMR, nuclear magnetic resonance; MALDI-TOF MS, matrix-assisted laser desorption/ionization time-of-flight mass spectrometry; LPS, lipopolysaccharide; NF- κ B, nuclear factor kappa-light-chain-enhancer of activated B cells; AMPK, AMP-activated protein kinase; TNF- α , tumor necrosis factor α ; iNOS, inducible nitric oxide synthase; COX-2, cyclooxygenase-2; IL-6, interleukin 6; MAPK, mitogen-activated protein kinases; IBD, inflammatory bowel disease; MMP-9, matrix metalloproteinase-9; VEGF, vascular endothelial growth factor

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1.2. Chitosan

Treatment of chitin with an alkali solution converts it into chitosan: a completely or partially deacetylated form of chitin. Chitosan can be defined as a natural, non-toxic biopolymer and a linear polysaccharide consists of β -1,4-GlcNAc and β -1,4-GlcN. Chitosan is water insoluble, but soluble in aqueous organic acid solutions (de Assis et al., 2010). Unlike chitin, chitosan is not a component in animal species and is rarely found in nature. Natural sources of chitin, including shells of crabs and shrimps, the bone plates of squids and cuttlefish do not contain chitosan, however, the fungi synthesize both chitin and chitosan in their cell walls (Nwe, Furuike, & Tamura, 2009). Chitosan is an important component of the cell wall of *Zygomycetes* (Chatterjee, Adhya, Guha, & Chatterjee, 2005). Chitosan is also naturally found in the mycelia, stalks, and spores of *Basidiomycetes*, *Ascomycetes*, and *Phycomycetes* (Logesh, Thillaimaharani, Sharmila, Kalaiselvam, & Raffi, 2012). Muzzarelli et al. (2012) have discussed in detail, the presence of both chitin and chitosan in the cell walls and septa of yeast and filamentous fungi.

Chitosan is present in two different forms in the cell wall of fungi: a free form of chitosan and chitosan bonded to glucan (Nwe et al., 2009). Methods are available for the direct extraction of chitosan from natural sources. The quality and quantity of chitosan acquired from fungal cell walls depend on the fungal species, fermentation conditions and the extraction procedures. Chitosans recovered from crustacean sources have a high molecular weight (MW) with low polydispersity, degree of N-acetylation (DA) below 20% and a 1% solution viscosity of 500–1700 cps. While fungal chitosan has a low MW with high polydispersity, DA lower than 15% and a 1% solution viscosity of 10–15 cps. (Nwe et al., 2009).

Commercial chitosan is mostly obtained from the deacetylation of natural chitin and its annual production is estimated to be several gigatons (El Kadib, 2016). The global market for chitosan is projected to exceed 118,000 tons by 2018 and a forecast suggests shortage of suppliers to meet this demand (Gómez-Ríos, Barrera-Zapata, & Ríos-Esteva, 2017). Annually, approximately 150,000 tons of industrially usable chitosan comes from the conversion of chitin obtained as a by-product of seafood processing. Most of the chitosan is used in cosmetics, organic fertilizers, and dietary supplements (Fernandez & Ingber, 2014).

Chitin and chitosan can be differentiated on the basis of amount of acetylation of the D-glucosamine units. Chitin contains more than 70% acetylated units, while chitosan has less than 30% acetylation. In the presence of organic acids such as formic acid, acetic acid and ascorbic acid, chitosan forms salt and consequently become water soluble (Uragami & Tokura, 2006). Chitosan contains three reactive functional groups, an amino- or N-acetamide group along with two primary and secondary hydroxyl groups at C-2, C-3 and C-6 positions, respectively. The key difference among the structure and physicochemical properties of different chitosans is of amino- or N-acetamide groups (Xia, Liu, Zhang, & Chen, 2011). The classification of chitosan can be carried out according to the fraction of N-acetylated residues (FA), DA, the degree of polymerization (DP), the MW, the MW distribution (PD or Polydispersity) and the pattern of N-acetylation (PA) or sequence (Aam et al., 2010). Chitosan offers great potential for the applications in various industries due to its distinctive physicochemical characteristics such as biocompatibility, biodegradability and low toxicity. Chitosan can be further hydrolysed into its low MW derivatives, which are biologically more active than chitosan.

1.3. Chitoooligosaccharides

Chitosan contains rather unstable glycosidic bonds, which make it cleavable by hydrolyzing agents to produce chitosan oligomers with variable DPs (Kim & Rajapakse, 2005). Chitosans with DP less than 20 and an average MW less than 3.9 kDa are called chitoooligosaccharides (COS), chitosan oligomers or chitoooligomers (Lodhi et al., 2014; Mahata

et al., 2014). COS possess a wide range of biological activities and have numerous promising applications in multiple fields such as medicine, cosmetics, food and agriculture (Dou et al., 2009; Fernandes et al., 2008). COS, being recognized as low MW and water soluble chitosans, have much greater demand than that of precursor molecule, which is justified by their growing commercial availability.

This review attempts to describe several biological activities of COS and the proposed molecular mechanisms behind these activities. The article exclusively discusses COS characteristic and also highlights the potential applications of COS in various industries with respect to their biological activities. Various commercially available COS products have also been presented in the paper.

2. Properties of COS

Chitoooligosaccharides generally consists of GlcNAc or GlcN units linked by β -1,4-O-glycoside bond. COS can be produced with defined DP and different DA, yet, their PA is always random (Hamer et al., 2015). Homochitoooligosaccharides are the oligomers of GlcN (D unit) or GlcNAc (A unit) and are exclusively composed of D or A units, while heterochitoooligosaccharides, comprising of both D and A units, are a combination of numerous oligomers varying in the DP, DA, degree of deacetylation (DD) and position of N-acetyl residues in the oligomer chain. Hetero-chitoooligosaccharides with DP less than 10 are typically water soluble, however, water solubility of COS with DP more than 10 depends on the DA and the pH of solution. The food industries, pharmaceutical industries and research scientists preferably use heterochitoooligosaccharides (Il'ina & Varlamov, 2015). COS consisting of a few monomer units are called oligomers, and the number of these monomeric units within an oligomer is designated as DP. Therefore, a tetra-saccharide (DP 4) is a lower oligomer of a penta-saccharide (DP 5). Different COS may have the same DP, but different FA (fraction of N-acetylated residues). Oligomers of the same DP (having same number of monomeric units), but different FA value are homologs. For example, penta-saccharide D4A1 (FA 0.2) is a lower homolog of penta-saccharide D2A3 (FA 0.6). Number of homologs comprising one oligomer is DP + 1. Given a particular homolog, isomers may exist that differ in the sequence of D and A units but have same DP and FA (Kim, 2010). The number of all compounds comprising one oligomer increases exponentially with the DP.

The DP of COS varies from 2 to 20 units in a segment, and each segment differs in the FA and in the sequences of D and A residues. Water solubility and lower viscosity of COS under physiological conditions are considered to be linked with their shorter chain lengths and free amino groups in D-glucosamine units (Bahrke, 2017). COS are insoluble in acetone, butanol, ethanol, ethyl acetate, propanol and pyridine but fully soluble in water and partially soluble in methanol and dimethyl sulfoxide. COS with DP 2–4 are soluble in methanol but with DP > 5 are poorly soluble (Mourya, Inamdar, & Choudhari, 2011). Like other sugars COS are sensitive to autooxidation and must be kept at ambient temperature in dry and inert conditions. For long-term storage the temperature should be kept below -20°C . The shelf life of COS is significantly increased when they are stored with antioxidants like vitamin C or salts like sodium chloride (Bahrke, 2017). Unlike chitin and chitosan some unique properties of COS such as water solubility, cell membrane penetrability, easy absorption and various biological activities make them extremely valuable product. Therefore, in recent times, COS have gained an increasing interest from an enormous number of researchers all over the world. It was found that COS with a relatively high DP (6 or higher) and low MW were more biologically active than oligomers with low DP and high MW (Prashanth & Tharanathan, 2007). Hence, it can be deliberated that DP and MW of COS are the principle characteristic and key factors, which directly affect their physicochemical properties and biological activities. The properties of COS with same DP may differ because of difference in DA or the arrangement of acetyl groups. Therefore, when complex mixtures of COS are

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