The Possible Roles of Chitosan and Its Derivatives in Cardiovascular Health: An Overview

Se-Kwon Kim¹²* and Dai-Hung Ngo¹

¹Marine Bioprocess Research Center, Pukyong National University, Busan 608-737, Korea
²Department of Chemistry, Pukyong National University, Busan 608-737, Korea

ABSTRACT

Cardiovascular diseases, principally atherosclerosis, stroke or myocardial infarction, are a significant public health problem worldwide. Attempts to prevent cardiovascular diseases often imply modifications and improvement of causative risk factors such as obesity, elevated blood pressure, an unfavorable lipid profile or insulin resistance. Chitosan and its derivatives are considered to promote diverse activities, including antihypertensive, antioxidant, antiinflammatory, anticoagulant, antitumor and anticancer, applications in drug delivery and acceleration of calcium and iron absorption, antimicrobial, hypocholesterolemic and antidiabetic effects. By modulating and improving physiological functions, chitosan and its derivatives may provide novel therapeutic applications for the prevention or treatment of chronic diseases. This review focuses on chitosan and its derivatives with biological activities relevant to cardiovascular health.

Keywords: Chitosan, Chitosan derivatives, Cardiovascular diseases, Antihypertension, Antioxidant, Anticoagulant, Antidiabetic

INTRODUCTION

Chitosan is a natural nontoxic biopolymer produced by the deacetylation of chitin, a major component of the shells of crustaceans such as crab, shrimp, and crawfish. Chitin and chitosan are insoluble in water as well as most organic solvents, which is the major limiting factor for their utilization in living systems. Hence, it is important to produce soluble chitin or chitosan by several methods such as acidic and enzymatic hydrolysis. Chitooligosaccharides (COS), partially hydrolyzed products of chitosan or chitin, are of great interest in pharmaceutical and medicinal applications due to their non-cytotoxic and high water soluble properties. Various activities of COS are affected by degree of deacetylation (DD) and molecular weight (MW) or chain length (1-3).

Currently, chitosan and its derivatives have attracted considerable attention for its commercial applications in the biomedical, food, and chemical industries due to their numerous biological properties, including antihypertension (4), antioxidant (5,6), anticoagulant (7), anticancer (8-10), antibacterial (11-15), antiinflammatory (16,17), calcium and ferrous binding agent (18,19) and hypocholesterolemic agent (20,21).

Cardiovascular diseases (CVD), principally atherosclerosis, stroke or myocardial infarction, are a significant public health problem worldwide. Attempts to prevent CVD often imply modifications and improvement of causative risk factors such as high blood pressure, obesity, an unfavorable profile of blood lipids or insulin resistance (22). By modulating and improving physiological functions, chitosan and its derivatives may provide novel therapeutic applications for the prevention or treatment of chronic diseases. This review centers on chitosan and its derivatives with properties relevant to cardiovascular health including antihypertensive, antioxidant, anticoagulant, hypocholesterolemic and antidiabetic effects.

ANTIHYPERTENSIVE ACTIVITY

Elevated blood pressure is increasingly prevalent in developed countries and one of the major independent risk factors for CVD (23,24). Angiotensin-I converting enzyme (ACE) plays a vital physiological role in the regulation of blood pressure by converting angiotensin-I to angiotensin-II, a potent vasoconstrictor. Therefore, the inhibition of ACE activity is a major target in the prevention of hypertension (25).

Researches on chitosan and its derivatives have identified their potential to inhibit ACE activity. COS derivatives such as carboxylated COS, hetero-COS, aminoethyl COS, chitosan trimer oligomers and chitin derivatives, have been reported as potent ACE inhibitors. A high-salt diet can raise blood pressure because Cl⁻ activates ACE, while chitosan can bind Cl⁻ and lower blood pressure (26). Hong et al. (27) studied ACE inhibitory activity of different COS and identified that chitosan trimer is more effective in lowering blood pressure compared to other oligomers. Specifically, the trimer has a lower IC₅₀ value (0.9 µM) than most of the other MW

*To whom all correspondence should be addressed
Tel: +82-51-629-7097; Fax: +82-51-629-7099; E-mail: sknkim@pknu.ac.kr
COS. Moreover, COS have remarkable ACE-inhibitory activity (28). The ACE inhibitory activity of hetero-COS was dependent on the DD and COS with relatively lower DD and medium MW (1–5 kDa) exhibited the highest ACE-inhibitory activity with the IC50 value of 1.22 μM and the inhibition pattern is competitive according to the Lineweaver-Burk plots. These findings suggested that MW and DD of COS are important factors for the ACE inhibitory activity.

Chitins with different DD have been chemically modified by grafting 2-chloroethylamino hydrochloride onto chitin at the C-6 position to develop ACE inhibitory chitin derivatives (29). Three kinds of chitin derivatives including, aminoethyl-chitin (AEC) with 10%, 50% (AEC50) and 90% (AEC90) DD were prepared having potential ACE activity. IC50 values of ACE were 0.064 μM (AEC), 0.038 μM (AEC50), and 0.103 μM (AEC90). In addition, AEC50 effectively decreased systolic blood pressure in spontaneously hypertensive rats (SHR) in a dose-dependent manner.

Carboxylated COSs is strong antihypertensive compound that shows equal activity to captopril (30). Carboxylated COS enhances the activity significantly with increased degree of substitution. Furthermore, Lineweaver-Burk plot studies showed that the inhibition was competitive via the obligatory binding sites of enzymes. Substitution of hydrogen atom at the C-6 position of the pyranose residue with the aminoethyl group promoted ACE inhibitory effect of COS.

In addition to the ACE, renin also plays an important role in the renin-angiotensin system. Renin (or angiotensinogenase), is a rate-limiting enzyme in the renin-angiotensin system. It cleaves plasma angiotensinogen to angiotensin-I, which is further converted by ACE to angiotensin-II. Therefore, the inhibition of renin effect is also an attractive target in hypertension therapy (32). Park et al. (33) reported that six kinds of COS with potent renin inhibitory activity were prepared using ultrafiltration membrane reactor. According to them, 90% deacetylated and medium MW (1–5 kDa) COS exhibits the highest renin inhibitory activity with IC50 value of 0.51 mg/mL, and acts as competitive inhibitor with Ki value of 0.28 mg/mL by Lineweaver-Burk and Dixon plots. Collectively, chitosan and its derivatives are novel therapeutic drug candidates for treat hypertension in pharmaceutical industry.

**ANTIOXIDANT ACTIVITY**

Humans are impacted by many free radicals both from inside our body and surrounding environment, particularly reactive oxygen species (ROS) generated in living organisms during metabolism. It is produced in the forms of H2O2, superoxide anion (O2•−) and hydroxyl radicals (·OH). In addition, oxidative stress may cause inadvertent enzyme activation and oxidative damage to cellular systems. Free radicals attack macromolecules such as DNA, proteins and lipids, lead to many health disorders including hypertensive, cardiovascular, inflammatory, aging, diabetes mellitus, neurodegenerative and cancer diseases. Antioxidants may have a positive effect on human health since they can protect human body against deterioration by free radicals (34,35). Recently, the antioxidant activity of chitosan and its derivatives attracted a greater attention due to their multiple potential activities and availability.

Antioxidant effect of chitin oligosaccharides (NA-COS) produced by acidic hydrolysis from crab shell chitin were evaluated. NA-COS can inhibit myeloperoxidase activity in human myeloid cells (HL-60) and decrease free-radical oxidation of DNA and membrane proteins. In addition, direct intracellular radical scavenging effect and intracellular glutathione level were significantly increased in the presence of NA-COS (36,37).

Gallic acid-grafted COS inhibited intracellular free radical-mediated oxidation. Gallic acid-grafted COSs can be used as a potential natural compound-based antioxidant in the functional food and pharmaceutical industries (38,39). Aminoethyl-COS possesses potential antioxidant activity, and can be used as a scavenger in controlling free radicals that lead to damage to cellular system (40,41).

The antioxidant activity of chitosan was studied in vitro and in vivo (42). Chitosan at an addition of 0.02% had antioxidant effects in lard and crude rapeseed oil but the activity was less than ascorbic acid. In the food industry, chitosan (edible chitosan, more than 83% DD) and COS have been used as dietary food additives and functional factors for their health beneficial effects as well as drug carriers.

Park et al. (43) prepared three kinds of partially deacetylated hetero-chitosans such as 90%, 75% and 50% deacetylated chitosan from crab chitin, and investigated their scavenging activities against 1,1-diphenyl-2-picrylhydrazyl (DPPH), alkyl, "OH, and O2•− radicals using electron spin resonance (ESR) spectrometer. The scavenging activities of hetero-chitosans increased from 3 to 69.39% with increasing concentration from 1.25 to 5 mg/mL of alkyl radical. In addition, 90% chitosan with relatively high DD showed the highest radical scavenging effects on the "OH, and O2•− radicals and the radical scavenging activities of these hetero-chitosans depend on their DD and concentration.

Yen et al. (44) reported that chitosan was prepared by alkaline N-deacetylation of crab chitin for 60 (C60), 90 (C90) and 120 (C120) min and its antioxidant effects determined. Chitosans exhibited antioxidant effects of 58.3–70.2% at 1.0 mg/mL, and reducing powers of 0.32–0.44 at 10 mg/mL. At 10