CHAPTER THREE

Antidiabetic Activities of Chitosan and Its Derivatives: A Mini Review

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Abstract

Obesity and diabetes are two important closely related matters to world health with increasing morbidity and mortality rate. Many recent studies promoted chitosan-based substances as lead molecules for treatment and prevention of obesity, diabetes, and related complications due to their easy and potential utilization in the food, pharmaceutical, agricultural, and environmental fields. Although detailed action mechanism and how chitosan-based molecules act as antidiabetics and antioesity specifically are remain to be enlightened, studies exhibited enough evidence to direct our intention to produce natural therapeutic agents using chitosan and its derivatives as lead substances. In this chapter, some reported antidiabetics and antioesity applications of chitosan and its derivatives have been briefly summarized in regard to acting pathways and structure-based activity in order to obtain some valuable insights into novel chitosan-based derivatives and their utilization for antidiabetic and antioesity purposes.

1. INTRODUCTION

Chitin is one of the most abundant carbohydrates worldwide and can be found in varying sources including bacterial cell walls and crustacean shells. As a derivative of chitin, chitosan is a functional and linear
carbohydrate prepared by N-deacetylation of chitin in the presence of alkaline. Generally, deacetylation cannot be completely achieved even under harsh treatment. The degree of deacetylation usually ranges from 70% to 95%, depending on the method used. Thus, chitosan is available with various molecular weights and deacetylation degrees. Chitosan is insoluble in water, alkali, and organic solvents but is soluble in most solutions of organic acids when the pH of the solution is below 6. The industrial production and application fields of chitosan have been steadily increasing since 1970s. Early applications of chitosan were centered on the treatment of wastewater, heavy metal adsorption, food processing, immobilization of cells and enzymes, resin for chromatography, functional membrane in biotechnology, animal feed, and so on. The recent trend is toward producing high-valuable industrial products such as cosmetics, drug carriers, and pharmaceuticals. Chitin and chitosan are known to exhibit antitumor, antibacterial, hypocholesterolemic, and antihypertensive activity (Kim & Rajapakse, 2005). The main motive for the development of new applications for chitosan lies in the fact that it is a very abundant polysaccharide, as well as nontoxic and biodegradable. Despite its functions and importance as a biomaterial, the applications of chitosan in food and biomedical industries are narrowed owing to its poor solubility, high molecular weight, and viscosity. There are evidences about the non- or poor absorption of chitin and chitosan in human intestine due to lack of enzymes to cleave the β-glucosidic linkage in chitosan. Since chitosan is a water-insoluble large biopolymer, it is difficult to be absorbed by human body. In this respect, enzymatic hydrolysis of chitosan to obtain oligomers is of great interest recently (Juon & Kim, 2000).

Chitosan oligosaccharides (COS) are hydrolyzed derivatives of chitosan composed of β-(1→4) d-glucosamine units. They have better properties such as lower viscosity, relatively smaller molecular size in comparison to chitosan, and short-chain length with free amino groups which makes COS highly soluble in aqueous solutions. COS are effective agents for lowering of blood cholesterol and pressure, controlling arthritis, and enhancing antitumor properties (Kim & Rajapakse, 2005). Since COS are biodegradable, water-soluble, and nontoxic compounds (Qiu et al., 2006), they might be beneficial biomaterials for diseases such as diabetes and obesity with increasing morbidity and mortality rates.

As a chronic disease, diabetes that occurs when beta-islet cells (pancreas) do not secrete enough insulin or the body cannot use insulin efficiently must be kept under control. Diabetic disorders, especially hyperglycemia can lead to serious damage to many parts of the body’s especially the nerves and blood
vessels (Vinik, Maer, Mitchell, & Freeman, 2003). The cause of diabetes is not fully known, although it is clearly shown that both genetic and environmental factors, especially obesity, appear to play important roles. Differentiated adipocytes secrete obesity-related factors called adipokines. Plasma leptin, tumor necrosis factor α, and nonesterified fatty acid levels are all elevated in obesity and play a role in causing insulin resistance (Leong & Wilding, 1999). Therefore, suppression and regulation of obesity can be achieved by inhibiting adipocyte differentiation and forcing adipocytes to lipolysis to reduce accumulated white adipose tissue (Langin, 2006; Yamachi et al., 2001). Thus, the increased control of the harmful effects of the accumulation of adipose tissue and its metabolism contribute to the search for a better understanding of the prevention of diabetes.

With a long onset and serious complications, which usually result in high morbidity rate, the treatment of diabetes is a major concern in all countries. Up to now, many kinds of antidiabetic medicines from natural resources have been developed for patients (Grover, Yadav, & Vats, 2002; Ivorra, Paya, & Villar, 1989; Koski, 2004; Li, Zheng, Bukuru, & De Kimpe, 2004), but most of these biochemical agents are not suited for mass production to meet to be a pharmaceutical agent. The natural compounds demonstrated a significant practice and show a bright potential in the treatment of diabetes and its complications with their naturally occurring structure and relatively less side-effects. In this respect, chitin, chitosan, and its derivatives with available large numbers of different chemical structures and bioactivities offer a great potential to recover and/or preventing obesity and diabetes.

2. DERIVATIZATION

Chitosan and its monomer glucosamine are highly derivatized recently in order to find new natural compounds with higher bioactivity than their predecessors (Fenton et al., 2000; Jiang et al., 2007; Prabaharan, 2008). Main derivatization of chitosan is forming soluble forms of chitin which makes it more biofriendly and easily absorbed by body after the oral administration (Hai, Bang Diep, Nagasawa, Yoshii, & Kume, 2003; Ilina & Varlamov, 2004; Kuroiwa, Ichikawa, Hirata, Sato, & Mukataka, 2002). Since, effectiveness of the compound, based on its absorption rate by body, this kind of derivatization is opened up new angles for chitin derivatization toward new bioactive compounds. In this respect, chitosan is the main derivative of chitin. Rather than the chitosan, COS are also highly bioactive derivatives of chitosan with significantly high absorption rates and water solubility.
Beside oligomerization, other main derivatization for chitin and its monomer glucosamine is adding negative and/or positively charged side chains. In this manner, glucosamine, chitin, chitosan, and COS reformed under chemical conditions to give sulfated, phosphorylated, carboxymethylated, deoxymethylated derivatives and so on (Cho, Lee, Kim, Ahn, & Je, 2011; Huang, Mendis, & Kim, 2005; Je & Kim, 2006; Kim, Kong, Pyun, & Kim, 2010; Kim et al., 2005; Kochkina & Chirkov, 2000). This high variety of derivatives comes with high variety of bioactivities, which changes in the effectiveness of compound in same bioactivity.

3. ANTI DIABETICS AND ANTI OBESITY APPLICATIONS

Chitosan-based products are known to have many biological activities such as antitumor, anti-HIV, antifungal, antibiotic, and against oxidative stress (Artan, Karadeniz, Karagozlu, Kim, & Kim, 2010; Kendra & Hadwiger, 1984; Kim et al., 2008; Nishimura et al., 1998; Xie, Xu, & Liu, 2001). Activities can be grouped in two according to use of chitin-based products. These products are highly used as indirect helping agents to enhance the effectiveness of other active compounds through chemical modification or nonchemical linkage against diabetes and obesity. On the other hand, the main role of chitin-based products, known as therapeutic nutraceutical agents, is to act directly against diabetes and obesity. In both cases, these natural product derivatives express high and significant potential in the light of searching bioactive pharmaceuticals against obesity and obesity-related diabetes.

3.1. Indirect activity

The preferred route of drug administration for patients is mostly the oral route on chronic therapy of diseases and complications. However, the oral delivery of many therapeutic peptides and proteins is still an unsolved problem basically because of the size, hydrophilicity, and unstable conditions of these molecules. Thus, several chitosan derivatives have been developed over the years with improved properties for enhanced applicability (Fernandez-Urrusuno, Calvo, Remunan-Lopez, Vila-Jato, & Alonso, 1999; Thanou, Verhoef, & Junginger, 2001). Therefore, recent studies focused on carrier products for administration of insulin efficiently in pre- or postdiabetic patients and lately one of these products is chitosan derivatives. It has been reported by Portero, Teijeiro-Osorio, Alonso, and
Remuñín-López (2007) that chitosan sponges are quite successful for buccal administration of insulin. Moreover, up-to-date studies presumed that chitosan-derived particles are highly usable for insulin administration by orally with their high protective effect and harmless structure (Hari, Chandy, & Sharma, 1996; Krauland, Guggi, & Bernkop-Schnurch, 2004, 2006). Results of some related studies have suggested that, the observed drug delivery activity of chitosan is highly promising in the case of insulin. For example, studies showed chitosan–insulin nanoparticles have strong affinity to rat intestinal epithelium after 3 h of postoral administration (Ma, Lim, & Lim, 2005). This suggests that chitosan as a cofactor for drug delivery makes insulin absorption safe and rapid. Carboxymethyl-hexanoyl chitosan is an amphiphilic chitosan derivative with important swelling ability and water solubility under natural conditions and studies showed these hydrogels can be used for encapsulating the poorly water-soluble drugs for efficient drug delivery (Lin & Lin, 2010) which lightens up the way for efficient insulin delivery by chitosan derivatives. Also, Mao et al. (2005) showed that PEG–trimethyl chitosan complexes are efficiently coupled with insulin and easily taken up by Caco-2 cells.

Beside drug delivery activity for insulin, studies have shown that chitosan complexes can be efficiently used for gene delivery for gene therapy (Koping-Hoggard et al., 2001). Therefore, it can be easily adduced that chitosan complex derivatives are potent gene delivery targets for high prevalent diseases such as diabetes. Furthermore, it has been reported that this chitosan complexes have relatively higher uptake and transfection efficiency than that of other polysaccharide complexes used for both drug and gene delivery (Huang, Khor, & Lim, 2004). Several researches prove chitosan as a nontoxic alternative to other cationic polymers and it gives a high potential for further studies of chitosan-based gene delivery systems (Sato, Ishii, & Okahata, 2001). All these results suggest that chitosan and chitosan-based derivatives are light upon the search of a nontoxic agent for drug and gene delivery, which is highly crucial for diabetic patient’s improved life standards.

Moreover, studies on streptozotocin (STZ)-induced diabetic rats expressed, beside treatment of diabetic patients, that chitosan-based sponges are highly effective against diabetic wounds. Wang et al. (2008) suggests that application of chitosan–collagen complex is an ideal wound-healing cover to enhance recovery of healing of wounds such as diabetic skin wound, which provides a great potential for chitosan and its derivatives to be used clinically for diabetic patients.
To conclude, chitosan-based polymers show great potential for treatment of diabetes therapeutically with their high efficient drug and gene delivery properties as well as effectiveness on diabetic wound healing.

3.2. Direct activity

Overweight and obesity are common health conditions worldwide that result in diabetes, but there are not so common treatments. Therefore, studies of chitosan are focused on its fat-lowering and fat-preventing activities. Several researchers have demonstrated that chitosan tends to bond with the ingested dietary fat and carry it out in the stool while preventing their absorption through the gut (Kanouchi, Deuchi, Imasato, Shizukuishi, & Kobayashi, 1995; Maezaki et al., 1993). Related researches about fat-lowering activity of chitosan also have shown that chitosan is capable of absorbing fat up to five times of its weight. In respect of these results, there are several studies showing chitosan derivatives lower the level of LDL while increasing the HDL levels. Studies of chitosan and its fat-lowering activity have expressed that chitosan and its derivatives as highly effective hypocholesterolemic agents with the ability of decreasing blood cholesterol level up to as much as 50% (Jameela, Misra, & Jayakrishnan, 1994). Moreover, diabetic patient-based studies clearly showed that daily administration of chitosan could drop the blood cholesterol levels by 6% with an increased level of HDL. In addition to chitosan, COS, oligomerized derivatives of chitosan, show high activity in regulating blood cholesterol levels. Especially, studies reported that COS are capable of regulating cholesterol levels even in liver. COS prevent development of fatty liver caused by the action of hepatotrope poisons. Despite few studies were carried out for the activities of COS in regulating blood cholesterol level mechanism, several of them suggested possible mechanism of COS lowering the LDL levels. As Reuman-Lopez, Portero, Vila-Jato, and Alonso (1998) suggested, ionic structure of COS binds bile salts and acids which inhibit lipid digestion through micelle formation. However, Tanaka et al. (1997) suggest a different mechanism of chitosan and COS where lipids and fatty acids are directly bonded by chitosan.

In addition to fat-lowering mechanisms of chitosan and its derivatives, studies have also proved that chitosan administration can be lead to increase the insulin sensitivity in animal models (Neyrinck et al., 2009). It has been shown that 3-month administration of chitosan significantly increased insulin sensitivity in obese patients and expressed a highly notable decrease in
body weight and triglyceride levels (Hernandez-Gonzalez, Gonzalez-Ortiz, Martinez-Abundis, & Robles-Cervantes, 2010).

On the other hand, glucosamine and its derivatives are reported to be highly effective against adipogenesis in vitro. Recent studies showed that phosphorylated derivative of glucosamine inhibited the adipogenesis of 3T3-L1 cells as well as fat accumulation. Several researches suggested that acetylated chitin treatment causes adipocytes to break down fats and lower their fat accumulation as much as half of control cells (Kong, Kim, Bak, Byun, & Kim, 2011). Kong, Kim, and Kim (2009) demonstrated clearly that sulfated derivative of glucosamine inhibited the proliferation and adipogenesis mechanism through AMPK pathways in 3T3-L1 cells. Glucosamine, acetylated-, sulfated-, and phosphorylated-glucosamine derivatives are reported as successful adipogenic inhibitors with high potential to prevent weight gain by adipogenesis in high diabetes-risk patients. As well as, it has been reported that COS inhibit the fat accumulation and adipogenesis in 3T3-L1 cell line (Cho et al., 2008). In addition, studies have shown that treatment with glucosamines reduced the triglyceride content of adipocytes and enhanced glycerol secretion as a lipid lowering effect. Most of these studies have expressed the better activity of chitosan-based compounds such as COS and glucosamines, after derivatization by adding a charged side chain by phosphorylation and sulfation. Therefore, it can be suggested that cationic power of glucosamine and COS plays the main role in their antiobesity effect. Further, a selective synthesis of phosphorylated or sulfated derivatives of chitosan and glucosamine will open up the way to a better understanding behind the structure–mechanism relation. However, up-to-date researches have strong proofs that antiobesity effect of chitosans effect through PPAR-γ pathway of adipogenic differentiation results in less adipocytes as adipose tissue and lipid accumulation. Collectively, chitosan and its derivatives such as glucosamines and COS successfully inhibit the differentiation of cells into adipocytes as well as enhancing adipocytes to hydrolyze the triglycerides which shows a significant effect against lipid accumulation in the body. This effect of chitosan and its derivatives demonstrates an important effect against obesity in the way leading to diabetes and shows great amount of potential to be used as pharmaceutical agents.

Additionally, chitosan and its oligosaccharides act as antidiabetic agents for treatment of diabetes in manner of protecting pancreatic beta-cells. In type 2 diabetes, although patients can retain healthy pancreatic beta-cells for many years after disease onset, chronic exposure to high glucose will impair beta-cell function in later stages. Impaired beta-cell functionality leads to cellular
damage in type 2 diabetic patients (Ibara et al., 1999). Therefore, the protection of beta-cells is of high importance for quality life of diabetic patients and elevated insulin secretion. Recent studies reported that COS as a protective agent for pancreatic beta-cells against high glucose-dependent cell deterioration (Karadeniz, Artan, Kong, & Kim, 2010). It is suggested that at the same time COS could effectively accelerate the proliferation of pancreatic islet cells with elevated insulin secretion in the aid of lowering blood glucose levels. Liu, Liu, Han, and Sun (2007) reported that COS treatment could improve the general situation and diabetic symptoms of diabetic rats, decrease the blood glucose levels, and normalize the impaired insulin sensitivity. Moreover, COS were reported as preventive agent in nonobese diabetic mice from developing type 1 diabetes, which might be related to several bioactivities of COS. These results supported the hypothesis that COS can prevent pancreatic beta-cells of diabetic patients and normalize the crucial insulin secretion. The mechanism behind this protection is studied and suggested as related to immunopotentiation and antioxidation activity of COS.

Renal failure is one of the most common diseases caused by diabetes mellitus. The metal crosslinked complex of chitosan, chitosan–iron(III), have been recently reported to be highly active for reducing phosphorus serum levels to treat chronic renal failure (Schoninger, Dall'Oglio, Sandri, Rodrigues, & Burger, 2010). This relatively new derivative of chitosan is significantly capable of adsorbing serum phosphorus in alloxan diabetes-induced rats with symptoms of renal failure progression.

Moreover, recent studies indicate that diabetics may be at higher risk for blood coagulation than nondiabetics. This life-threatening condition urges to be treated for diabetic patients. Therefore, sulfated derivative of chitosan has been shown to possess anticoagulant potency (Vongchan, Sajomsang, Subyen, & Kongtawelert, 2002). Furthermore, studies have reported that sulfated chitosan does not show antiplatelet activity unlike heparin which is an efficient anticoagulant agent. Collectively, results proved that sulfated chitosan is a more efficient agent than that of heparin, although heparin has been used for a long time for blood coagulation treatment.

In addition to COS, chitosan also reported to prevent the progression and symptoms as well as the complications of low-dose STZ-induced slowly progressive non-insulin-dependent diabetes in rats (Kondo, Nakatani, Hayashi, & Ito, 2000). Briefly, reports suggest that chitosan-based products protect pancreatic cells and insulin secretion mechanism in diabetic conditions. Furthermore, these compounds could decrease the progression and
complication rate of diabetes onset in animal models, given that chitosan-based products have a great potential to be used as a nutraceutical for the treatment of diabetics.

4. CONCLUSION

High mortality and morbidity of diabetes make diagnosis, preventing, and treatment more important as more and more patients are diagnosed by diabetes in the world in recent years. Beside diabetes, factors relating to diabetes such as obesity and damaged pancreatic cells must be kept under control in order to prevent diabetes onset. In this manner, chitosan and its derivatives possess various biological activities and have a remarkable potential to be used in several of therapeutic applications. Thus, many of the studies carried out to search antidiabetic activities of chitosan-based compounds provide detailed acting mechanisms and activity for prevention and/or treatment of diabetes-based complications. Chitosan and its derivatives such as COS and glucosamines as monomers express high activity in manner of lowering lipid accumulation and cholesterol as well as pancreatic beta-cell prevention. In addition, studies proved that chemical modification of these compounds could express better activity and understanding of mechanism lying behind antidiabetic effects. Therefore, future researches should be directed to enhance the effectiveness of chitosan-based compounds in order to gain more active and less harmful agents. Collectively in conclusion, these evidences suggest that chitosan-based agents are highly potent nutraceuticals for treatment and prevention of diabetes and diabetes-related complications.

REFERENCES


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