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Chitosan And Its Derivatives: Unveiling Their Potential In Anti-Diabetic Therapy

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ABSTRACT: Diabetes mellitus, the most prevalent endocrine disorder, is characterized by chronic high blood sugar due to inadequate insulin production or insulin resistance. Despite advances in treatment, diabetes remains a major contributor to global morbidity and mortality, and currently, there is no definitive cure or preventive measure available. Given the long-term negative impacts of the disease, traditional pharmacological treatments are often insufficient for prolonged management. In contrast, chitosan and its derivatives offer significant promise in various medical applications due to their diverse biological activities. They exhibit notable anti-diabetic properties, such as inhibiting α-amylase and α-glycosidase activities, enhancing glucose metabolism, and alleviating β-cell dysfunction. These compounds help preserve pancreatic cell integrity, boost insulin secretion, reduce insulin resistance, and improve gut microbiota balance, thereby effectively mitigating diabetes and hyperglycemia. Moreover, chitosan and its monomers, like chitosan oligosaccharides (COS) and glucosamine, have shown strong effects in reducing fat accumulation, lowering cholesterol levels, and modulating pancreatic beta cell development. Studies also indicate that chemical modifications to these molecules can further enhance their efficacy, shedding light on the mechanisms behind their anti-diabetic benefits. Overall, the evidence highlights the potential of chitosan-based compounds as powerful neutraceuticals for both preventing and treating diabetes and its related complications.

Keywords: Hyperglycemia, Chitosan, α-amylase, Glucosamine, α-glycosidase.

1. Introduction:

Diabetes poses a significant global health challenge, affecting millions of individuals worldwide at an alarming rate. As per the 9th edition of the IDF Diabetes Atlas, more than half a billion people (comprising 9.3% of adults aged 20–79 years) are afflicted by diabetes globally as of 2019. (1) Diabetes mellitus encompasses a range of metabolic conditions marked by persistent high levels of blood sugar, resulting from inadequate insulin production, impaired insulin action, or a combination of both factors. (2) Diabetes mellitus (DM) is typified by elevated blood glucose levels, stemming from disrupted glucose regulation due to immune-mediated insulin deficiency (Type 1 DM, T1DM), or a combination of insulin resistance and impaired insulin secretion (Type 2 DM, T2DM). (3) Polysaccharides are extended carbohydrate polymers consisting of monosaccharide units linked by glycosidic bonds. These bioactive macromolecules are obtained from various sources such as plant materials or crustacean shells. (4) Polysaccharides exert their anti-diabetic effects through several mechanisms, including the protection of pancreatic islet β cells to prevent apoptosis, improvement of insulin sensitivity, modulation of glucose metabolism signaling pathways, and enhancement of gut microbiota activity to regulate oxidative and inflammatory stress. (5)

2. The anti-diabetic impact and mechanism of action of chitosan and its derivatives:

Chitin is a polysaccharide similar to cellulose, composed of repeating linear β-(1,4) N-acetyl-D-glucosamine (GlcNAc) monomers. Chitosan, which is obtained from the partial deacetylation of chitin under alkaline conditions, is a random copolymer consisting of N-acetyl-D-glucosamine and D-glucosamine units. (7) The degree of deacetylation (DD) determines the proportion of D-glucosamine units within chitosan. Different types and molecular weights (MW) of chitosan have been explored to investigate their effects on human and animal health. Research indicates that their biological properties are significantly influenced by factors such as MW, DD, degree of polymerization (DP), and distribution of charges. (8) Chitosan oligomer, abbreviated as COS, is derived from the hydrolysis of chitosan or chitin through enzymatic or chemical processes involving deacetylation and depolymerization. In recent times, COS has emerged as a promising natural therapeutic agent, offering excellent solubility and absorbability characteristics, along with diverse biological functionalities. (10)

Chitosan, a promising polysaccharide, has garnered significant research interest due to its multitude of confirmed beneficial effects, including the protection of pancreatic beta cells, reduction of hyperglycemia, anti-oxidative, anti-inflammatory, gut regulating effects and prevention of impaired lipid metabolism associated with diabetes mellitus. (9)

2.1 The impact of molecular weight on absorption and the anti-diabetic properties:
The molecular weight (MW) of water-soluble chitosan significantly affects intestinal absorption. Once absorbed from the small intestine into the bloodstream, COS is primarily transported to the liver, kidney, and spleen through a combination of carrier protein assistance and free diffusion. Although lysozyme present in the blood, liver, kidney, and urine can decrease the MW of absorbed COS, unabsorbed COS may reach the distal intestine and be metabolized and utilized by gut bacteria. (11)

2.2 Preservation of pancreatic beta-cell function and enhancement of insulin secretion:
Pancreatic β-cells are crucial for regulating glucose levels. Impairment of these cells can result from inadequate expansion of beta-cell mass and insufficient insulin supply. COS may safeguard pancreatic β-cells by enhancing the activity of antioxidative enzymes or acting as scavengers for free radicals. Moreover, COS not only protected pancreatic cells but also stimulated insulin secretion. In experiments with primary cultured rat pancreatic cells, COS was observed to augment insulin production. (12)

2.3 Inhibition of carbohydrate-hydrolysing enzymes:
Carbohydrate-digesting enzymes like α-amylases and α-glucosidases found in mammals are essential for breaking down digestible carbohydrates into monosaccharides such as glucose and fructose, facilitating their absorption into the bloodstream. Inhibiting the activities of these enzymes to a certain extent can help stabilize increases in blood glucose levels. Water-soluble derivatives of chitosan have been documented to exhibit anti-α-amylase and anti-α-glucosidase properties. (6)

2.4 Facilitates glucose uptake and storage in peripheral tissues:
The inability of peripheral tissues to effectively absorb and utilize glucose can lead to persistent high levels of glucose in the bloodstream. Dysfunctions in Glucose transporter 4 (GLUT4) can contribute to insulin resistance and impaired glucose tolerance. (13) Both low- and high-molecular-weight chitosan promote the uptake of glucose by muscles by facilitating the translocation of GLUT4 from the cytoplasm to the cell membranes in STZ-induced T1DM rats. This process may be mediated by increased phosphorylation of AKT. Moreover, COS significantly enhances glycogen synthesis in the liver by boosting the activity of glucokinase, suggesting that COS facilitates the storage of more blood glucose in the liver as glycogen. (14)

2.5 Mitigates Insulin Resistance:
Insulin resistance is a key factor in the onset of T2DM and is considered a hallmark of the disease. Treatment with COS has been shown to effectively improve overall health, alleviate symptoms, normalize blood glucose levels, and enhance insulin sensitivity in diabetic rats. (15)

3. Conclusion:
Diabetes continues to be a major global health issue, significantly contributing to both morbidity and mortality. Despite persistent efforts, a definitive prevention or cure remains elusive. Recent research, however, indicates that chitosan and its derivatives show potential in managing diabetes by improving glucose and lipid homeostasis in diabetic animal models. These compounds help alleviate diabetes by inhibiting the enzymes α-amylase and α-glucosidase, enhancing glucose metabolism, and reducing β-cell dysfunction. They contribute to the preservation of pancreatic β cells, increase insulin production, lower insulin resistance, and positively alter gut microbiota, which together help mitigate diabetes mellitus and hyperglycemia. Additionally, chitosan and its derivatives have been found to activate insulin signaling pathways, particularly the PI3K/Akt pathway. It is essential to develop environmentally sustainable methods for synthesizing these derivatives to minimize ecological impact. Nonetheless, further evidence from both animal studies and clinical trials is urgently required to better understand their effects on glucose regulation and overall safety.

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