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Original Article

Impacts of chitosan and its nanoformulations on the metabolic syndromes: a review

Impactos da quitosana e suas nanoformulações nas síndromes metabólicas: uma revisão

M. E. Abd El-Hack[a]*, M. Kamal[b], R. S. Alazragi[c], R. M. Alreemi[c], A. Qadhi[d], K. Ghafouri[d], W. Azhar[d], A. M. Shakoori[e], N. Alsaffar[f], H. M. Naffadi[g], A. E. Taha[h] and S. A. Abdelnour[i]

[a]Zagazig University, Faculty of Agriculture, Department of Poultry, Zagazig, Egypt
[b]Agricultural Research Center, Animal Production Research Institute, Dokki, Giza, Egypt
[c]University of Jeddah, College of Science, Department of Biochemistry, Jeddah, Saudi Arabia
[d]Umm Al-Qura University, Faculty of Applied Medical Sciences, Clinical Nutrition Department, Makkah, Saudi Arabia
[e]Umm Al-Qura University, Faculty of Applied Medical Sciences, Laboratory Medicine Department, Makkah, Kingdom of Saudi Arabia
[f]Mohammed Al-Mana College for Medical Sciences, Biochemistry and Molecular Biology Department, Dammam, Saudi Arabia
[g]Umm Al-Qura University, College of Medicine, Department of Medical Genetics, Makkah, Kingdom of Saudi Arabia
[h]Alexandria University, Faculty of Veterinary Medicine, Department of Animal Husbandry and Animal Wealth Development, Edfina, Egypt
[i]Zagazig University, Faculty of Agriculture, Department of Animal Production, Zagazig, Egypt

Abstract

A significant public health issue worldwide is metabolic syndrome, a cluster of metabolic illnesses that comprises insulin resistance, obesity, dyslipidemia, hyperglycemia, and hypertension. The creation of natural treatments and preventions for metabolic syndrome is crucial. Chitosan, along with its nanoformulations, is an oligomer of chitin, the second-most prevalent polymer in nature, which is created via deacetylation. Due to its plentiful biological actions in recent years, chitosan and its nanoformulations have drawn much interest. Recently, the chitosan nanoparticle-based delivery of CRISPR-Cas9 has been applied in treating metabolic syndromes. The benefits of chitosan and its nanoformulations on insulin resistance, obesity, diabetes mellitus, dyslipidemia, hyperglycemia, and hypertension will be outlined in the present review, highlighting potential mechanisms for the avoidance and medication of the metabolic syndromes by chitosan and its nanoformulations.

Keywords: chitosan, nano chitosan, metabolic syndrome, obesity, diabetes.

Resumo

Uma questão significativa de saúde pública em todo o mundo é a síndrome metabólica, um conjunto de doenças metabólicas que compreende resistência à insulina, obesidade, dislipidemia, hiperglicemia e hipertensão. A criação de tratamentos e prevenções naturais para a síndrome metabólica é crucial. A quitosana, juntamente com suas nanoformulações, é um oligômero de quitina, o segundo polímero mais prevalente na natureza, criado por desacetilação. Devido às suas abundantes ações biológicas nos últimos anos, a quitosana e suas nanoformulações têm despertado muito interesse. Recentemente, a entrega de CRISPR-Cas9 baseada em nanopartículas de quitosana tem sido aplicada no tratamento de síndromes metabólicas. Por isto, os benefícios da quitosana e suas nanoformulações na resistência à insulina, obesidade, diabetes mellitus, dislipidemia, hiperglicemia e hipertensão serão delineados na presente revisão, destacando potenciais mecanismos para evitar e medicação das síndromes metabólicas pela quitosana e suas nanoformulações.

Palavras-chave: quitosana, nano quitosana, síndrome metabólica, obesidade, diabetes.

1. Introduction

Chitosan has numerous health benefits, including its potent antioxidant and antibacterial properties and it's being a non-antigenic, biocompatible, non-toxic, and eco-friendly natural polymer formed from chitin (Chou et al., 2015; Muxika et al., 2017; Guan et al., 2019). While many polysaccharides are neutral or anionic in charge, chitosan is a naturally occurring cationic polymer. Using further synthetic polymers or naturally negatively charged natural materials, this chitosan characteristic enables the construction of multilayer structures or electrostatic complexes (Venkatesan and Kim, 2010). Additionally, chitosan has many biological abilities, such as antibacterial (Amato et al., 2018; Wei et al., 2019), anticancer, and antioxidant properties (Karagozlu and Kim, 2014; Ngo and Kim, 2014). Chitosan is widely employed in a diversity of biomedical and biological uses, such as a platform for genetic manipulation (Islam et al., 2020), a drug carrier (Peers et al., 2020), and water purification (Das et al., 2020).

*e-mail: dr.mohamed.e.abdalhaq@gmail.com
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Moreover, chitosan has special potential that makes it safe for usage in biomedical, therapeutics, and wastewater remediation, where chitosan and its derivatives are considered viable sources for creating efficient and secure medication delivery systems because of their unique physical and chemical features (Abd El-Hack et al., 2020). Likewise, in the utmost available investigation, many previous investigational data disguised that the growth-enhancing properties of chitosan are equivalent to those of dietary antibiotics (Kamal et al., 2023b, a) indicating that chitosan is a practical and operative antibiotic additional.

Nano chitosan is a natural molecule with brilliant physicochemical and biological actions, constructing it a greater naturally friendly substance, and it holds bio-competence action that levels safe on a human being. In addition, it's commonly utilized as a controlled-release drug transporter for genetic editing in synthetic tissues and immune syndromes. Besides, nano chitosan has been utilized to impart antimicrobial benefits and increase the forte and washability of textiles (Ting and Shen, 2005). Nanosized materials are good, but their impacts on natural organisms and human organs have been investigated. Polysaccharide-coated nanoparticles are recognized to be ecologically kind, much less related to physiological stability, and concerns over toxicity and biodegradability. For instance, chitosan, a natural polysaccharide, is widely used in medical preparations (Swierczewska et al., 2016; Shariatinia, 2019).

Chitosan has been generally applied for protein encapsulation, therapeutically enzymes (Koyani et al., 2018), or as biocatalytic nanoparticles (NPs) (Alarcón-Payán et al., 2017). Although non-toxic and biodegradable, chitosan nanoparticles are recognized to accomplish prolonged gradual emancipation of the capacity, escalation bioavailability, and enhance therapeutic effectiveness (Safdar et al., 2019). To benefit from the affluence usefulness of manufacturing, great revenue at squat cost, and greater loading capability, the manufacturing procedure for nanoparticles such as chitosan NPs might be enhanced (Gallego et al., 2019; Kamel and El-Sayed, 2019). According to (Quester et al., 2022), chitosan-based nanoparticles comprising α-lipoic acid could pass the gastrointestinal barrier and emancipate their antioxidant consignment while remaining stable in stomach-like circumstances.

The incidence of metabolic disorders, a conglomeration of metabolic illnesses comprising obesity, insulin resistance, hyperglycemia, hypertension, and dyslipidemia, is estimated to be 25% worldwide (Eckel et al., 2005; Saklayen , 2018). Over time, many administrations, comprising the World Health Organization, the International Diabetes Federation, and the National Cholesterol Education Program Adult Treatment Panel III, have created varied clinical criteria for various metabolic syndromes (Huang, 2009). Thus, the danger of metabolic disease for cardiac ailment and type 2 diabetes is becoming more widely acknowledged (Hudish et al., 2019). Pharmacological treatments and lifestyle changes are the predominant approaches for metabolic disorders (Saboya et al., 2017; Larsen et al., 2018). Drugs are frequently employed since, in many situations, changing one's lifestyle may not yield the optimum results. Therefore, these medications have various adverse effects, including myalgia, hypoglycemia, and gastrointestinal discomfort. Their restricted use is also due to their high price (Ramkumar et al., 2016; Wang and Hoyte, 2019). Therefore, the search for natural remedies to lower the jeopardy and development of metabolic disorders has gained more and more attention. The antibacterial, immunostimulatory, hypoglycemic, anti-inflammatory, anti-obesity, hypolipidemic, anti-oxidative, and anti-hypertensive abilities of chitosan and its nanoformulations have been the substance of numerous research (Naveed et al., 2019; Khalaf et al., 2023). Chitosan and its nano formulations may be a potential natural product to prevent delicacy metabolic disorders.

According to Herdiana et al. (2023), one of the primary causes of cancer worldwide, breast cancer, frequently results in the creation of reactive oxygen species (ROS) and oxidative stress. This emphasizes the need for antioxidants to maintain the immune system and cell health. Natural antioxidants are crucial in lowering oxidative stress and restoring the body's internal environment equilibrium. Due to their weak solubility, 80 percent have limited effectiveness when taken orally. Increasing solubility in water is one tactic. Systems of chitosan-based nanoparticles are investigated because of their consistency and ease of manufacture. They can serve as a paradigm for developing natural antioxidant oral dosage forms that are effective and enhance the efficacy of cancer drugs. Cancer is one of the top causes of death, according to ALaqeel (2024), but patients are not always fit for current therapies, and they frequently have negative effects. The field of functional foods has witnessed a surge in the creation of natural anti-cancer medications, as several molecules have demonstrated both effectiveness and low toxicity. Due to their high flavonoid content, citrus peels may be able to prevent cancer. These antioxidants enhance apoptosis, prevent metastatic chain reactions, reduce the motility of cancer cells, and inhibit vasculature.

Body mass index (BMI) values are markedly elevated in obese individuals, although a slightly elevated BMI can boost overall survival and therapeutic responses (Berger, 2014). The "obesity paradox" states that when a person's BMI reaches the threshold of morbid obesity, the preventive benefits of a moderately elevated BMI disappear. It is still unclear how a person's degree of morbid obesity affects how their body reacts to cancer treatment (Lennon et al., 2016). The increased bulk of adipose tissue could be a sign of energy reserves that help certain patients withstand the damaging effects of chemotherapy for a longer period. Longer lifetimes could be made possible by increased adipose storage, which could act as an energy reserve (Sánchez-Jiménez et al., 2019).

In this criticism, we will discuss the indication for the favorable abilities of chitosan and its nanoformulations on obesity, hyperglycemia, diabetes mellitus, dyslipidemia, and hypertension based on the *in vivo* and *in vitro* tests. We will also discuss the promising mechanisms of chitosan and its nanoformulations' avoidance and management of the metabolic syndrome.

2. Chitosan Structure

Chitosan is a polysaccharide molecule derivative from the chitin compound. It's a common naturalistic polymer present in the cell walls of fungi and many exoskeletons such as arthropods, shellfish, and some insects (Nwe et al., 2009; Ahsan et al., 2018). Different sources of chitosan and chitin are depicted in Figure 1. The unique structure of its free amino group, chitosan, is more capable of chemical changes and has better water solubility and hydrophilicity. Chitosan is manufactured by handling chitin with a determined NaOH solution, which fulfills N-deacetylation (Dutta et al., 2004; Negm et al., 2020).

Because it permits unique biological roles and the utilization of alteration responses, the attendance of amine clusters in chitosan and chitin is a significant benefit (Kumar, 2000). These polysaccharides' exceptional qualities, including their biocompatibility, non-toxicity, biodegradability, bioresorptivity, bioactivity, and worthy adsorption actions, make them ideal biomaterials and attract a lot of industrial interest as potential substitutes for synthetic polymers (Tan et al., 2009; Croisier and Jérôme, 2013). The physicochemical possessions of chitosan are restricted by the molecular weight (MW) and further the N-deacetylation proportion. The more frequently employed expression is DA, which characterizes the percentage of N-acetylgluchitosanamine monomers to the whole numeral of polymer elements. As recounted by (Benediktsdóttir et al., 2014), the D-A of a polymer such as chitosan can differ, but it is frequently arranged more than <50%

3. Chitosan Derivatives

The biological and physicochemical possessions of chitosan can be improved chemically. Chitosan has limited water solubility, and another prevalent organic solvent is one of its principal problems; however, this can be fixed chemically. Additionally, adding additional moieties to the polymer chain can enhance chitosan's other features, increasing its employment for medicinal requests (Negm et al., 2020). Chitosan derivatives can be produced using diverse synthetic approaches comprising direct modification, enzymatic processes, and chemical grafting (Nagy, 2018). The focal worry is that some functional clusters might obstruct the reaction and produce undesirable byproducts. So, they use shielding groups that briefly cover the functional clusters that would otherwise conflict (Carey and Sundberg, 2007).

Wuts and Greene (2006) reported that the molecule can add protective groups and withdraw without affecting the result. To provide a stable and sheltered substrate, a worthy defensive group must, among other things, react selectively with the required efficient cluster to produce an invention with a satisfactory yield. Chitosan has three nucleophilic functional clusters—the main\\O. H. group at the C-6 position, a secondary\\O. H. group at the C-3 position and an -NH_2 group at the C-2 position.

Applying protecting clusters on the extremely reactive hydroxyl moieties is sought to create novel moieties on the amino responsibility of chitosan abilities. Since organic chemical reactions frequently involve hydroxyl protecting groups, there are many hydroxyls protective techniques accessible.

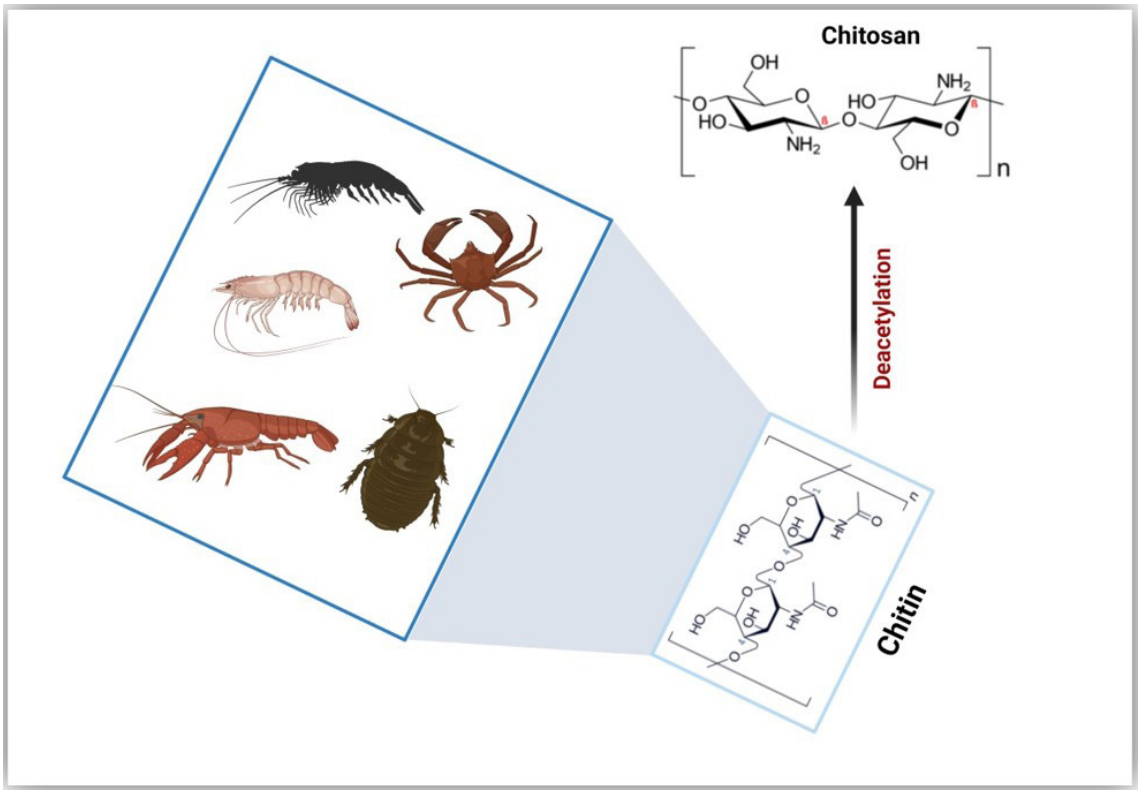

Figure 1. Different sources of chitosan and chitin.

The secondary – O.H. group of chitosan cannot be protected because the triphenylmethyl group can only be added to the primary\\O. H. group. Three synthesis steps are also included in the process, which is done at 100°C (Benediktsdóttir et al., 2011).

Wuts and Greene (2006) indicated that TMS (trimethylsilyl) and TBDMS (tert-butyldimethylsilyl) ethers of silyl are simply formed from hydroxyl groups. In contrast, TBDMS ethers are stable and satirically hindered protective groups that show promise. Using TBDMS protection groups, (Kurita et al., 2002; Nagy, 2018) created an artificial method to shield the hydroxyl clusters of chitosan. To create a completely 3,6-O-TBDMS protected chitosan, the TBDMS moiety is added to the mesylate salt of chitosan in one phase of the technique. Applying protecting groups to the amino group of chitosan is anticipated to create novel moieties on the hydroxyl responsibility of the substance where chitosan is created when polyamines precipitate in alkaline liquids. Even though it offers medicinal qualities like ulcer-fighting (Fini and Orienti ,2003), wound-healing (Azad et al., 2004), and antibacterial capabilities as well as the capacity to lower cholesterol (Sugano et al., 1988). Chitosan's R-NH_3^+ group, which are cationic, have mucoadhesive properties when it interacts with the negatively charged groups on mucosal surfaces (Kockisch et al., 2003). Also, protein-associated tight junctions endure revocable structural remodeling in response to interactions with protonated amine groups, which are followed by tight junction openings. The simplicity structure of chitosan may be chemically altered, notably in the C-2 position, causing derivatives with numerous possessions and possible uses, which is another feature that sets chitosan apart from other polysaccharide polymers (Huo et al., 2010). Likewise, Bashir et al. (2022) showed that owing to their exquisite biological characteristics, extensibility, and efficient consumption by intranasal mucosal cells to tumor cells.

Furthermore, chitosan and its nano derivatives could participate significantly in metabolic syndromes drug delivery. Developing anticancer medications, catalysis, gene delivery, sensor requests, packaging and wrapping supplies, cosmetic fabrics, and bioimaging is also progressing industrially for chitosan and its derivatives. The different possessions of chitosan and its derivatives make it a brilliant biomolecule for countless biomedical uses as revealed in Figure 2.

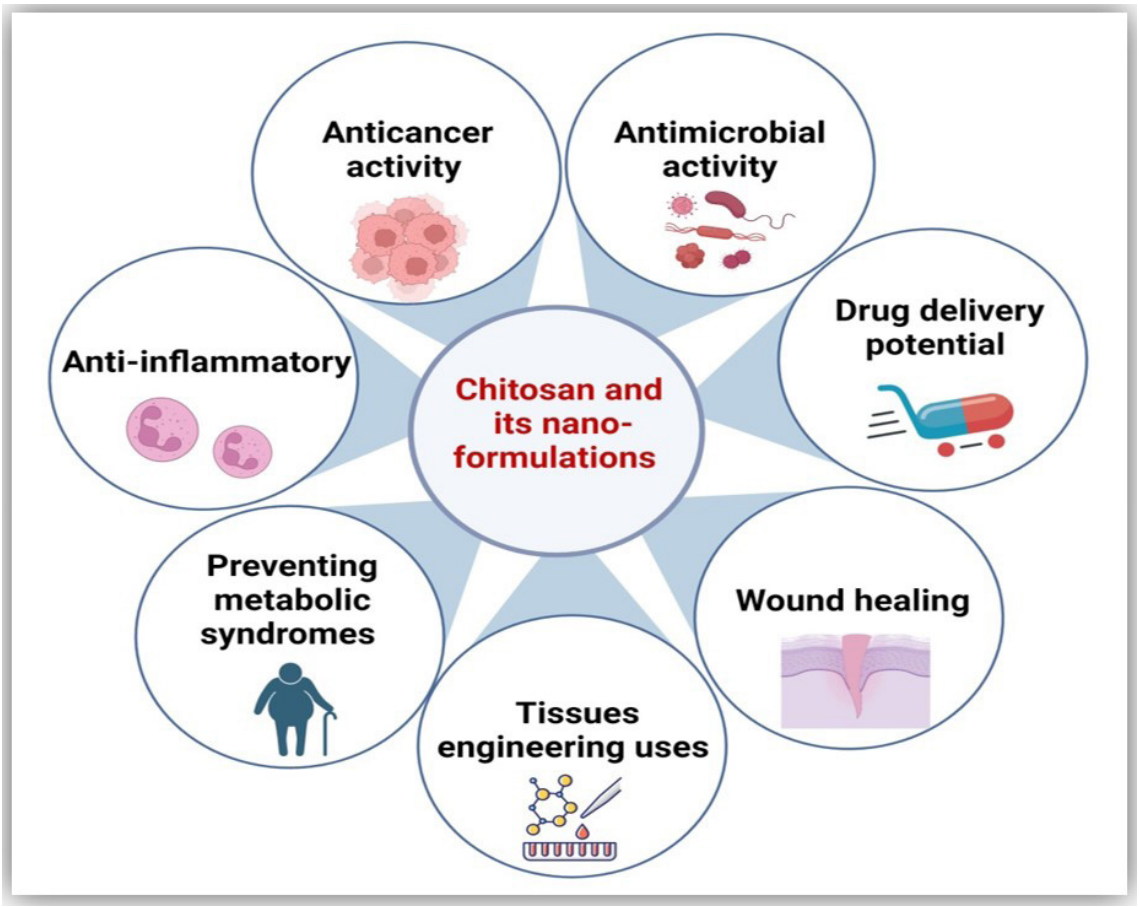

Figure 2. Biomedical uses of chitosan and its derivatives.

4. The Production of Chitosan Nanoparticles

Chitosan nanoparticles were initially stated in 1994 when (Ohya et al., 1994) anticipated consuming them to deliver the anticancer prescription 5-fluorouracil intravenously. These synthesized nanoparticles were formed by cross-linking and emulsifying chitosan. Meanwhile, these schemes have experienced considerable exploration for drug delivery tenacities. The innovative formularization has either been modified by utilizing various preparation procedures or for other uses, such as integrating active ingredients in toothpaste (Calvo et al., 1997; Erbacher et al., 1998; El-Shabouri, 2002; Liu et al., 2007a). Furthermore, numerous teams have formed fresh chitosan nanoparticle inventions with accompanying matrix-shaping machinery (Sarmento et al., 2006; Grenha et al., 2010).

Frequent approaches have been generated, primarily connecting emulsification, numerous coacervations, or even tiny variations. More specifically, the devices comprise desolvation (Tian and Groves, 1999), reverse micellar method (Orellano et al., 2017), ionic gelation, polyelectrolyte complexation (Sarmento et al., 2006), emulsion solvent diffusion (El-Shabouri, 2002), emulsion droplet coalescence (Tokumitsu et al., 1999), and All of these techniques fall under the category of bottom-up manufacture manners, which entail the gathering of compounds in solution to create specific structures, in this instance, nanoparticles (Chan and Kwok, 2011).

Bottom-up technologies frequently exhibit size polydispersity in their delivery systems, which might occasionally limit the effectiveness of nanoparticles (Wang et al., 2011). Chitosan, or one of its derivatives, is employed to make chitosan NPs. Because of chitosan's special non-toxicity, polymeric cationic nature, biodegradability, mucoadhesive chitosan, great biocompatibility, and absorption-enhancing properties, the N-deacetylated derivative of chitin is a desirable biopolymer for making nanoparticles (Kunjachan et al., 2010). Chitosan is advantageous in creating nanoparticles due to its cationic character, which permits ionic cross-related with multivalent anions (Agnihotri et al., 2004), and its linear polyamine structure, which has a diversity of free amine clusters that are reachable for cross-linking.

Chitosan NPs have distinct properties that enable *in vivo* site-specific targeting and increased affinity for negatively charged biological membranes (Qi et al., 2004). As a result, they can be employed for an assortment of requests in different industries to load medicines efficiently, enzymes, and nucleic acids (Colonna et al., 2007) using a controlled release (Corradini et al., 2010). Because of the characteristics of the material and the manufacturing process, chitosan nanoparticles exhibit excellent chemical, morphological, and physical capabilities. Chitosan is soluble in acidic solutions like citric, tartaric, and acetic acids but insoluble in water (Furuike et al., 2017). It comes in low- and high-molecular-weight varieties with weights stretching from 3800 to 20,000 Da. Chitosan's characteristics are substantially prejudiced by its molecular weight and level of deacetylation, especially when it comes to the creation of nanoparticles. Chitosan-based polymeric drug carriers, growth factors, anticancer medications, anti-inflammatories, antimicrobials, peptides, and other therapeutics have all been efficaciously administered (Sun et al., 2007).

Othman et al. (2018) indicated that the hydrophilic L-ascorbic acid and hydrophobic thymoquinone, a myriad of greatly effective multifactorial with inferior systemic intake, could be encapsulated collected in chitosan NPs schemes to escalate their therapeutic competence by indirectly participating to the improvement of pharmaceutical and medical areas. Also, pharmaceuticals can be delivered orally, transdermal, or intravenously using NPs as carriers. According to studies, chitosan NPs have been extensively employed in the medical and biological fields to remedy conditions like cancer (Nayak et al., 2016) and diabetes (Wong et al., 2017).

5. Metabolic Syndromes

With modernization and globalization, people's lifestyles have been meaningfully rehabilitated, comprising less leisure and more employed hours. Furthermore, the persistent usage of electronic gadgets has prepared the lifestyle softly and increased the generation of diseases. One of the prevalent ailments is metabolic syndrome (Azad et al., 2004), which is a cluster of pathologies such as insulin resistance, obesity, dyslipidemia, hyperglycemia, and hypertension, that make susceptible to cardiovascular diseases (Nakhaei et al., 2019; Rossi et al., 2022). Even though prevailing international clusters have assembled to elucidate a consent characterization of "metabolic syndrome," the identical has not been fulfilled for describing "metabolic dysfunction," a purport demonstrating disordered metabolism on a continuum rather than a definitive diagnosis. According to the pathophysiology reports of MS, augmented insulin resistance, plasma-free fatty acids, inflammation indices, and oxidative stress are the main underlying features of MS (Rossi et al., 2022). Insulin is an indispensable element for tissue uptake of glucose, deterring lipolysis and hepatic gluconeogenesis. Higher circulatory free fatty acids (FFAs) can conquer insulin consent, which is connected with insulin resistance in obese persons (Fahed et al., 2022).

Moreover, protein kinase activity is repressed with circulating FFAs; this feature can lower muscle glucose consumed. Contrariwise, greater hepatic protein kinase levels boost the assembly of atherogenic ingredients, counting glucose, LDL, and TGs. Furthermore, the resultant hyperglycemia activates more insulin releasing, thus causing hyperinsulinemia. Oxidative stress is also involved with insulin resistance and can prevent adipocytes from producing adiponectin (Furukawa et al., 2004). The connection between belly fat in insulin resistance is considerable as lipolysis of belly fat leads to boosted circulation of FFAs to the hepatic, triggering the amplified synthesis of TGs and LDL (Nakhaei et al., 2019). Besides, visceral adipose tissue triggers greater levels of plasminogen activator inhibitor, augmenting heparin-binding epidermal growth factor- and prothrombotic state that vascular modeling and encourages smooth muscle cells (Slate-Romano et al., 2022).

Previously, the association between MS and inflammation has been well documented through visceral obesity, which exaggerates insulin resistance. In this regard, the adipose tissue macrophages release TNF-α, which encourages the inactivation of insulin receptors in the thesis's tissues, instigating lipolysis with the synthesis of FFAs, thus preventing the emancipating of adiponectin (Nakhaei et al., 2019). Based on literature and clinical reports, there is a substantial connection between elevated amounts of TNF-α, obesity insulin and resistance (Wisse, 2004). The immune and adipocyte cells release IL-6 (interleukin-6), and its synthesis escalations with adipose tissue mass (Rocha et al., 2022), which further encourages the hepatocytes to create C-reactive proteins, whose raised level has been involved with the etiology of MS (Devaraj et al., 2009). Moreover, it is also involved in stimulating RSA pathways (Wisse, 2004).

6. Impacts of Chitosan and Its Nanoformulations on Obesity and Dyslipidemia

Obesity is a persistently sustained metabolic condition described by an extreme buildup of body fat brought on by an unbalanced energy intake. Additionally, dyslipidemia describes unhealthily high levels of one or more lipid types in the blood, including higher levels of triglycerides and LDL (low-density lipoprotein) and reduced levels of HDL (high-density lipoprotein cholesterol), resulting from several abnormalities in structure, metabolism, antiatherogenic lipoproteins and biology of atherogenic (Srikanth and Deedwania, 2016). Chitosan has been established in numerous kinds of research to have effective anti-obesity and hypolipidemic properties. Furthermore, it has been shown that chitosan successfully suppressed hypertrophy and adipocyte hyperplasia in HFD (high-fat diet)-stimulated obese rat models (Bai et al., 2018; Pan et al., 2018; He et al., 2020; Lee et al., 2021). It also decreases body weight growth, hepatic fat gathering, blood lipid levels, hypertrophy, and adipocyte hyperplasia.

One of the major health issues associated with modern wealthy society is obesity. In 2015, 2 billion adults worldwide—or 38-40% of the global population—were classified as overweight or obese (GBD, 2017). Several persistent illnesses, including breast cancer (BC), have greater rates of death and morbidity when an individual is obese. The elderly population has a rising rate of obesity (Shekhar et al., 2021; Fang et al., 2022). According to Chen et al. (2022), estrogen and inflammatory are associated with fat accumulation and hypertrophy, which may contribute to the occurrence of BC in postmenopausal women. Uncertainty surrounds the function of adipose tissue in cancer patients, though. Patients who are somewhat overweight fare better from treatment, illuminating the "obesity paradox." Weight control and prevention programs should be added to current treatments, and a tailored medical strategy should consider adiposity reduction. Liu et al. (2023) state that mitochondria are essential organelles for synthesizing energy, cell metabolism, and signaling. They also play a role in the growth and spread of tumors. Biology and synthesis in cancer cells can be enhanced by mutations in mtDNA and the tricarboxylic acid cycle (TCA) enzymes. Because mitochondria rely on glycolysis and oxidative phosphorylation for energy, they are the focus of cancer treatment. Targeting these pathways and metabolism may be a useful treatment approach for several malignancies.

The importance of mitochondria in carcinogenesis was highlighted by Kaelin Junior and McKnight (2013), who also discussed how their metabolites affect gene expression and cell signaling through epigenetic controls. The basic function of mitochondria is energy production. Furthermore, metabolites in the TCA have been shown to promote epigenetic alterations such as DNA methylation and post-translational modification of histones (Liu et al., 2022). These alterations control how histones interact with chromatin remodeling complexes and DNA. The tumor microenvironment can alter cell fate through epigenetic control. Tumors can be targeted by mutations in important TCA cycle metabolic enzymes, and cell proliferation can be inhibited by inhibitors that target cancer stemness. Designing treatments for the diagnosis and treatment of cancer can be aided by knowledge of carcinogenesis, mitochondrial metabolites, and epigenetics.

According to Abdullah et al. (2024), broiler weight gain and feed conversion ratio (FCR) were enhanced by feeding copper nanoparticles at a dose of 15 mg/kg. Furthermore, it has enhanced the bone and muscular features of broilers.

Chitosan has also been shown to lessen plasma lipids and increase body weight in mice (Kumar et al., 2009). Furthermore, Kamal et al. (2023a) described that the chitosan 0.2 g/kg diet enhanced the serum triglyceride and HDL, improving the health profile of NZW rabbits in Egyptian environments. The suppression of adipogenesis machinery is one method for avoiding and managing obesity.

In vitro trials demonstrated that chitosan could constrain the differentiation of 3T3-L1 preadipocytes and lessen fat gathering by decreasing the transcripts of PPAR-γ (peroxisome proliferator-activated receptor γ) and CCAAT enhancer-binding proteins α (C/EBP α), which are the main adipogenesis-associated transcription features (Cho et al., 2008; Kong et al., 2017). Additionally, chitosan reduced the transcript of associated elements in 3T3-L1 adipocytes, comprising leptin, adiponectin, resisting, FAS (fatty acid synthase), FABP (fatty acid binding protein), and GLUT4 (glucose transporter 4); (Rahman et al., 2008; Lee et al., 2021).

Remarkably, Bahar et al. (2013) described that chitosan repressed the de-methylation of leptin gene promoter in 3T3-L1 adipocytes, representing that chitosan decreased the differential of adipocytes via epigenetic machinery. Additionally, suppression of the PPAR-signaling way was one of the methods by which chitosan prevented hypertrophy and adipocyte hyperplasia in HFD-fed rats by controlling the transcriptomic related to lipogenesis in the adipose tissue (Huang et al., 2015; Pan et al., 2018).

According to an *in vitro* investigation, chitosan stimulated the PPAR γ signaling pathway to reduce fat formation in HepG2 cells exposed to palmitic acid (Bai et al., 2018). Also, chitosan has been shown to be efficient in reducing hepatic lipid accumulation, hepatic steatosis, and serum activities of both aspartate and alanine aminotransferases in obese rats or mice generated by HFD (Liu et al., 2018; Tao et al., 2019).

Chitosan enhanced intestinal barrier anomalies and dysbiosis of the gastro-microbiota in mice on an HFD, according to research by (He et al., 2020). Notably, the release of LPS (lipopolysaccharide), a constituent of the cellular structure of Gram-negative bacteria, into the blood to promote inflammation resulted from intestinal epithelium malfunction and dysbiosis of microbiota (Cani and Jordan, 2018). Furthermore, chitosan was found to reduce inflammatory blood markers, hepatic, fat tissues, and colon of HFD-triggered obese rats or mice, according to several research (Bai et al., 2018; He et al., 2020). These results mention that chitosan and its nano-formulation might be utilized to prevent or treat dyslipidemia and obesity.

The potential role of chitosan and its nano-formulation may inhibit adipogenesis, control liver lipid metabolism, enhance intestinal barrier malfunction, and dysbiosis of the gut microbiota (Figure 3). Moreover, Chen et al. (2020) found that rosuvastatin-loaded chitosan nanoparticles are more effective in depressing blood fat than clean rosuvastatin. Its assistance in macerating the calcification of different valve tissues in rabbit models. Also, Luo et al. (2021) presented that the management of chitosan NPs resulted in inferior blood LDL, total cholesterol, and uric acid. Furthermore, Abd-Elhakeem et al. (2016) signposted that giving rats chitosan and chitosan NPs reduced body weight gain and serum cholesterol levels.

In the same context, Oksal et al. (2020) mentioned that the chitosan-*Pandanus tectorius* fruit extract nanoparticles could decline the total cholesterol, LDL, and triglyceride amounts but also escalate the HDL amounts. Also, chitosan-*Pandanus tectorius* fruit extract nanoparticles will likely be applied as a novel unconventional management for hypercholesterolemia via the SR-B1 path. Additionally, Sriamornsak and Dass, (2022) mentioned that chitosan and chitosan NPs could be utilized to create various medication formulations. They also naturally lower cholesterol. As illustrated in Table 1, we summarized some trials on the favorable impacts of chitosan and nano-formulation on obesity and dyslipidemia.

7. Impacts of Chitosan and Its Nanoformulation on Hyperglycemia and Diabetes Mellitus

Diabetes mellitus is distinguished by chronic hyperglycemia caused by unbefitting secretion or incompetent uptake of insulin (Kharroubi and Darwish, 2015). The anti-diabetic action of chitosan has been presented using different diabetic models. The management of chitosan enhanced the broad state and diabetic indications, diminished the amounts of glucose in the blood and urine, as well as regularized decreased glucose tolerance in newborn STZ (streptozotocin)- triggered type 2 diabetic in rats, a model of non-insulin- entrusted diabetes mellitus (Liu et al., 2009). Ju et al. (2010) demonstrated that in insulin-resistant rats produced by a high-energy diet combined with STZ, chitosan administration for eight weeks led to diminished fasting insulin amounts and fasting blood glucose, further elevated insulin sensitivity directory and enhanced oral glucose tolerance.

According to Katiyar et al. (2011), chitosan significantly improved renal dysfunction and blood glucose control in alloxan-induced diabetic rats. Chitosan has also been shown to be inferior to blood glucose in mice (Zheng et al., 2018).

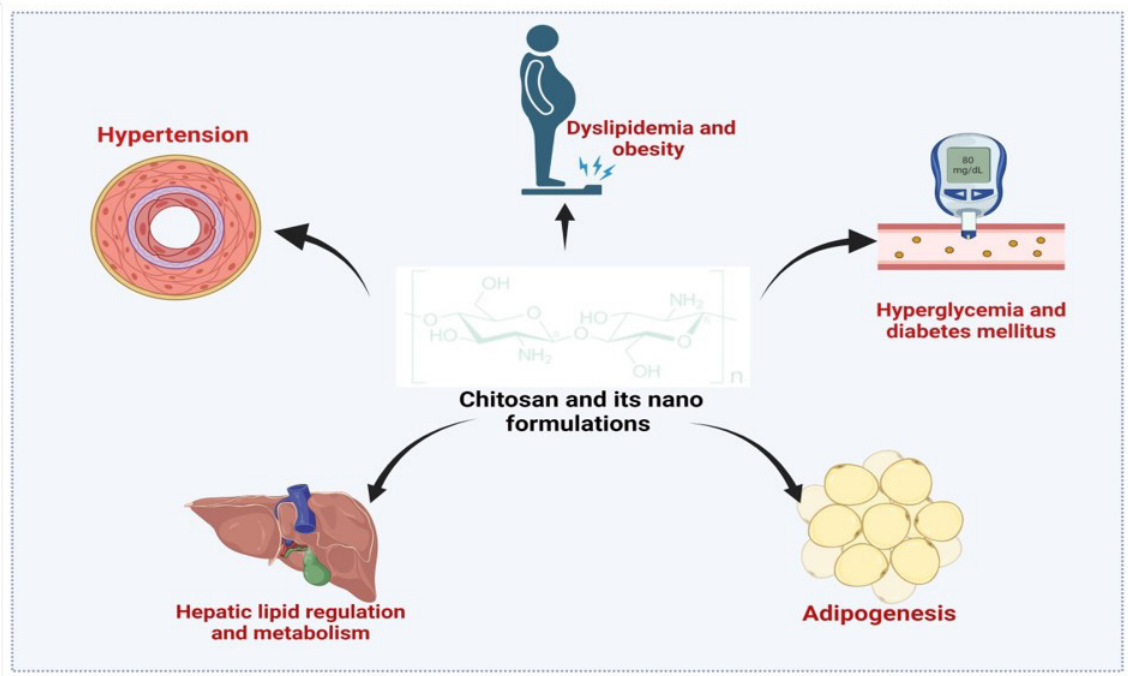

Figure 3. Medical role of chitosan nanoparticles.

Table 1. Summary of some studies on the beneficial effects of chitosan and nano-formulation on obesity and dyslipidemia.

Study Mode	Additive/dose	Findings	References
In vitro model	COS (1-3 kDa)	COS decreased lipid accumulation. Inhibited adipocyte differentiation.	Cho et al. (2008)
Mice	200 mg/kg of COS	COS can control diet intake, body weight gain, blood glucose, and lipid profiles.	Kumar et al. (2009)
In vitro model	1, 10, 100, 500 and 1000 μg mL^{-1}	COS inhibited the differentiation of 3T3-L1 preadipocytes.	Kong et al. (2017)
Rates	COS capsules	COS capsules can regulate body weight gain, lipids, and serum alanine aminotransferase.	Pan et al. (2018)
Mice	L MW COS(400 mg kg^{-1})	COS regulated the dysfunctional gut microbiota and alleviated low-grade inflammation	He et al. (2020)
Rats	GO2KA1 (200 to 800 μg/mL)	GO2KA1 may prevent diet-induced weight gain. Inhibited adipogenesis.	Lee et al. (2021)
Rabbits	0.2 g/kg of chitosan	Chitosan increased triglyceride and HDL, improving the health status of NZW rabbits.	Kamal et al. (2023a)
chickens	14-28 g/kg of COS	COS increased the relative weight of the liver. Increased HDL and decreased abdominal fat.	Zhou et al. (2009)
Rates	5% chitosan /kg	Chitosan reduced the absorption of dietary fat and cholesterol *in vivo*. Improve hypercholesterolemia.	Zhang et al. (2008)
Rates	450 mg/kg/day of CHNPs	CHNPs decreased body weight gain and serum lipid levels.	Abd El-Hack et al. (2020)
Rabbits	TPP Tween-80 Chitosan Ionotropic gelation	Drug-loaded NPs significantly lowered blood lipid levels compared to pure drug	Chen et al. (2020)
In vivo	Selenium Chitosan Chemical reduction	Reduced atherosclerotic lesions in ApoE-/-mice. Inhibited hyperlipidemia.	Xiao et al. (2021)
in vivo	NaTPP+Tween Chitosan powder	Reduced triglycerides and LDL. Increased HDL.	Oksal et al. (2020)

COS = chitosan oligosaccharides; GO2KA1 = the supplementation of low molecular chitosan oligosaccharide; CHNPs = chitosan nanoparticles; TPP = tripolyphosphate; NaTPP = chitosan and sodium tripolyphosphate; NZW = New Zealand white rabbits; NPs = Nanoparticles; HDL = High density lipoprotein; LDL = Low dinesity lipoprotein; MW = Molecular weight.

In Korean patients between the ages of 20 and 75, a chitosan addition of 1.5g per day for three months effectively lowered the postprandial serum glucose amounts, according to Kim et al. (2014a). Additionally, Yuan et al. (2009) described that chitosan reduced the damage of pancreatic islets, nuclear pyknosis of pancreatic cells, and atrophy of pancreatic cells in STZ-triggered diabetic rats. Additionally, *in vitro* research has demonstrated that chitosan can enhance pancreatic cell line apoptosis caused by STZ and stimulate cell growth (Ju et al., 2010). Yuan et al. (2009) indicated that chitosan increased the levels of superoxide dismutase and total antioxidant capability and depressed the amount of malondialdehyde (MDA) in the serum of STZ-triggered rats.

Karadeniz et al. (2010) also showed that chitosan could have free radical scavenging properties to defend against the oxidative stress that hydrogen peroxide (H2O2) causes in cells. These results imply that chitosan may serve as a free radical scavenger or improve the antioxidant competence to protect pancreatic cells. It can be inferred that chitosan's ability to lower oxidative stress and prevent human islet amyloid polypeptide aggregation makes it an effective antidiabetic medication (Meng et al., 2020).

Insulin resistance is one of the first signs of diabetes. Chitosan has decreased insulin resistance, which is mentioned to lower sensitivity and responsiveness to insulin in board tissues such as the hepatic, adipocytes, and skeletal muscle tissues (Czech, 2017). Ju et al. (2010) revealed that chitosan supplementation increased the insulin sensitivity marker and glucose tolerance in high-energy diet-paired STZ-triggered diabetic mice. Additionally, mouse research found chitosan dramatically reduces insulin resistance (Zheng et al., 2018). Numerous essential elements of the insulin signaling pathway, comprising the insulin receptor substrate, insulin receptor, phosphoinositide 3-kinase, and Akt, have been identified (James et al., 2021). By blocking the actions of glucoamylase and intestinal sucrose and decreasing the mRNA transcript of the sucrase-isomaltose complex in mice, long-term supplementation with chitosan dramatically diminished the amounts of glycated hemoglobin A1c and blood glucose (Kim et al., 2014b). A study by Jo et al. (2013) described that chitosan diminished the SI multifaceted mRNA transcript and hindered the glucosidase activities in human intestinal cells.

Chitosan is suitable for use because of its precautionary, biodegradability, biocompatibility, strong adhesiveness, ease, and permeability in the intestinal region (Souto et al., 2019). Additionally, it is known that chitosan-based nanoplatforms can deliver anti-cancer medications (Jaiswal et al., 2021). There are signs that chitosan-based nanoparticles containing oleic acid can protect insulin from being degraded by enzymes (Elsayed et al., 2010). Also, applying a complexing manager in chitosan nanoparticles improved insulin absorption (Lin et al., 2007; Chuang et al., 2013).

To increase hydrophilicity, mucoadhesiveness, and permeability in an alkaline media, chitosan derivatives such as thiolated chitosan, trimethyl chitosan, carboxylated chitosan, etc., were utilized in the production of nanoparticles (Wong et al., 2017). Additionally, at a pH of 7.4, it was found that trimethylated chitosan nanoparticles linked with insulin were steadier with constant insulin statements (Mi et al., 2008).

According to Abd El-Hameed (2020), the new polydatin-coated (POL) chitosan-nan nanoparticle formulation is biocompatible. It may gradually improve diabetic rats' nephropathy compared to free POL. The research also found that POL-nanoparticles have nephroprotective activity on diabetic nephropathy may be owing to its antidiabetic capability via the elevation of insulin secretion, regulation of HbA1c and blood glucose, (1) blocking oxidative stress synthesis through its antioxidant upshot and dropping AGEs creation, (2) its function as an anti-inflammatory mediator, and (3) The greatest beneficial effect of POL chitosan nanoparticles may be accredited by improving absorption and prolonged-release possessions.

The study of Salem et al. (2021) informed that chitosan nanoparticles could enhance the deficiency of fat metabolism as powerfully related to transcriptomics alterations correlated with lipogenesis and oxidative markers. Additionally, camel yogurt with 2% chitosan nanoparticles had good sensory and microbiological quality. Likewise, according to a study, 20 mg/kg of chitosan and nano-chitosan in guinea pigs dramatically decreased fasting blood glucose and enhanced renal function (Sami et al., 2022). According to Zhang et al. (2021), nano chitosan-zinc supplementation can enhance piglet small intestine antioxidant capacity and growth performance, reducing weaning stress. Chandrasekaran et al. (2020) reported that both G^- and G^+ bacteria are inhibited by the biological use of chitosan nanoparticles, alone or in combination with other chemicals. Also, Zhang et al. (2012) reported that cationic chitosan might increase the strong adhesiveness of polylactic-co-glycolic acid nanoparticles in the GIT.

Additionally, Adetunji et al. (2022) showed that nanoparticles significantly function in drug delivery to delicacy various metabolic syndromes. In the remedy of different sicknesses, including cancer and metabolic disorders, nanomaterials can potentially reduce the dosage of medications or their negative side effects. All these findings might suggest that chitosan and chitosan NPs can prevent diabetes by preventing the enzymes that break down carbohydrates in the intestine. According to in *vivo* and in *vitro* investigations, the beneficial effects of chitosan and nano-formulation on diabetes mellitus and hyperglycemia are illustrated in Table 2.

Table 2. Summary of some studies on the beneficial effects of chitosan and nano-formulation on diabetes mellitus and hyperglycemia.

Study Mode	Additive/dose	Findings	References
Pigs	1000 ppm chitosan	Chitosan exhibited anti-obesogenic potential through alterations to appetite and feeding behavior affecting satiety signals.	Egan et al. (2016)
Man	chitosan capsules (500 mg)	Reduced the mean body weight by up to 3 kg during the 90-day study period.	Trivedi et al. (2015)
		Improvement in body composition, anthropometric parameters, and improvement in quality-of-life score.	
Pigs	1000 ppm chitosan	Chitosan has affected potent anti-obesity/body weight control.	Egan et al. (2015)
Mice	COS (1.0 mg/mL, dissolved in water, about 200 mg/kg/d)	Improved glucose metabolism.	Zheng et al. (2018)
		Reshaped the unbalanced gut microbiota of diabetic mice.	
Mice	COS	Reduced the aggregation of hIAPP.	Meng et al. (2020)
		COS protected -cells from cytotoxicity of amyloidogenic hIAPP.	
Mice	GO2KA1 (MW< 1000 Da)	GO2KA1 may prevent diabetes type 2, via the inhibition of carbohydrate hydrolysis enzymes.	Kim et al. (2014b)
Rats	COS, (125-250 µg/25 µl, daily)	COS has antidiabetic.	Katiyar et al. (2011)
		COS has antihyperlipidemic and antioxidative activities.	
Rats	COS, 500 mg/kg	COS reduced fasting blood glucose.	Ju et al. (2010)
		COS increased the insulin sensitivity index and improved oral glucose tolerance.	
In vitro	chitosan NPs (100-500 nm)	Enhanced the general situation and diabetic symptoms.	Liu et al. (2007a)
		Reduced the levels of blood and urine glucose.	
In vitro	Insulin loading on NPs with chitosan.	Reduced the blood glucose level in a diabetic.	Lin et al. (2007)
Rats	CN (3 mg kg^{-1})/day	CN improved the impairment of lipid metabolism.	Salem et al. (2021)
Pigs	2% of nano-chitosan	Nano-chitosan reduced fasting blood glucose.	Sami et al. (2022)
		Chitosan and nano-chitosan improved the function of the kidney (urea and creatinine) in diabetic nephropathy.	
Piglets	CP-Zn (5-10% zinc and 50-60% chitosan)	CP-Zn increased the activity of carbohydrate digestion-related enzymes and mRNA expression.	Zhang et al. (2021)
		CP-Zn improved the antioxidant capacity of the jejunum by activating the Nrf2 signaling pathway.	

CP-Zn = nano chitosan-zinc complex; CN = chitosan nanoparticles; COS = chitooligosaccharides; GO2KA1 = the supplementation of low molecular chitosan oligosaccharide; hIAPP = human islet amyloid polypeptide; NPs = Nanoparticles; MW = Molecular weight; Nrf2 = nuclear factor erythroid 2-related factor 2.

8. Impacts of Chitosan and Its Nanoformulation on Hypertension

Cardiovascular illness, chronic renal disease, and cognitive impairment are all conditions that are thought to be significantly increased by hypertension (Iadecola and Gottesman, 2019; Fuchs and Whelton, 2020). Heredities, the stimulation of the RAAS (renin-angiotensin-aldosterone system), the stimulation of the sympathetic nervous scheme, endothelial dysfunction, vascular remodeling, insulin resistance, and defective ion channels are specific the elements linked to the pathophysiology of hypertension (Oparil et al., 2003). According to one of the investigations, a single oral dosage of chitosan trimer (2.14 mg/kg) effectively lowered blood tension in impulsively hypertensive rat models. Chitosan's ability to lower blood pressure may be connected to its ability to suppress RAAS and alleviate endothelial dysfunction.

Chitosan reduced ACE (angiotensin-I converting enzyme) activities at different polymerization levels (DP), ranging from 1 to 10 (Park et al., 2008). The chitosan trimer (DP = 3) displayed all the oligosaccharides' strongest inhibitory action. Additionally, the MW (molecular weight) degree of DD (deacetylation) of chitosan affects its ability to inhibit ACE. Chitosan with a regular MW of 1-5 kDa has greater ACE restrained action than chitosan with a regular MW of <1 kDa or 5-10 kDa (Park et al., 2003).

Liu et al. (2007b) stated that chitosan decreased intracellular oxidative markers, suppressed the construction of MDA, restored the actions of cellular antioxidants, increased levels of NO (nitric oxide) and NO synthase, and decreased cell apoptosis to decrease H_2O_2-triggered oxidative stress in endothelial cells. Also, Li et al. (2014) demonstrated that chitosan reduced the O-GlcNAc transferase-dependent NF-B's O-GlcNAcylation, inhibiting LPS-induced vascular endothelial inflammatory response. These results demonstrated that chitosan might ameliorate endothelial dysfunction and exhibit an anti-hypertensive effect by reducing inflammation and oxidative stress.

Accordingly, Tao et al. (2021) mentioned that chitosan has useful impacts on different metabolic syndromes constituents, including hyperglycemia, diabetes mellitus, obesity, dyslipidemia, and hypertension. According to Sharma et al. (2018), the study's encouraging findings validated the possible use of chitosan in preparing nebivolol-loaded chitosan NPs. Additionally, chitosan-coated polymers are recommended to facilitate oral management by enhancing the drug's solubility (Niaz et al., 2016). Like other polymeric nanoparticles (PNPs), Chitosan-based polymers have extended-release capabilities that can boost medicinal efficacy without increasing drug dosage, preventing negative side effects. Also, Chadha et al. (2012) presented that chitosan PNPs could treat hypertension caused by deoxycorticosterone acetate salt in rats *in vivo*. Additionally, Auwal et al. (2018) reported that chitosan PNPs protecting food-based antihypertensive biopeptides against gastrointestinal degradation are a secure and possibly appealing source of nonpharmaceutical treatment of treatment-resistant hypertension. Furthermore, Chinh et al. (2018) demonstrated that polylactic acid/chitosan nanoparticles carried the Ca2+ channel blocker nifedipine to inferior animal blood tensions.

In the other study, Auwal et al. (2017) found that ACE-inhibitory biopeptides stabilized by chitosan nanoparticles can successfully lower blood tension in hypertensive people for a protracted duration. In Table 3, we demonstrated the main findings of some investigations on the valuable effects of chitosan and nano-formulation on hypertension in Table 3.

Table 3. Summary of some studies on the beneficial effects of chitosan and nano-formulation on hypertension.

Study Mode	Additive/dose	Findings	References
Rats	chitosan trimer (2.14 mg/kg)	Chitosan reduced blood pressure in spontaneously hypertensive rat models	Hong et al. (1998)
In vitro	COSs with different MW and DD	The DD value and MW of COSs are important factors affecting renin-inhibitory activity.	Park et al. (2008)
Mice	COS	Chitosan might ameliorate endothelial dysfunction and exhibit an anti-hypertensive effect.	Li et al. (2014)
Rats	5% high-MW chitosan	Used as pharmacotherapies or as a dietary fiber against hypertension, dyslipidemia, and obesity	Chiu et al. (2017)
Mice	chitosan oligosaccharide	Chitosan has useful effects on various components of metabolic syndrome, including obesity, dyslipidemia, diabetes mellitus, hyperglycemia, and hypertension.	Tao et al. (2021)
Rats	Lecithin/CHNPs loaded with HCT	NPs increased the onset and duration of antihypertensive activity in DOCA-salt-induced hypertensive rats conclusively demonstrating the improved therapeutic efficacy of HCT when formulated as NPs.	Chadha et al. (2012)
Mice	CHNPs Loading Nifedipine	The polylactic acid/CHNPs loading nifedipine is suitable to apply in the treatment of hypertension.	Chinh et al. (2018)
Rats	CHNPs fabricated by ionotropic gelation	The ACE-inhibitory biopeptides stabilized by chitosan nanoparticles can effectively reduce blood pressure for an extended period in hypertensive.	Auwal et al. (2017)
In vitro	Captopril loaded CHNPs	Reported antihypertensive nano-cuticles based on chitosan improved the oral administration of currently available hydrophobic drugs while providing an extended-release function.	Niaz et al. (2016)
	SBs loaded Chitosan	The nanoparticles revealed sustained cumulative release for 12 h and improved efficacy with ACE-inhibitory.	Auwal et al. (2018)
Humans *In vitro*	Nebivolol loaded CHNPs	Chitosan nanoparticles enhanced the oral bioavailability of nebivolol and other lipophilic drugs.	Sharma et al. (2018)

CHNPs = chitosan nanoparticles; ACE = angiotensin I-converting enzyme; SPs = the stone fish biopeptides; HCT = hydrochlorothiazide; DOCA = Deoxycorticosterone acetate; DD = degree of deacetylation; MW = molecular weight; COSs = chitooligosaccharides; NPs = Nanoparticles; SBs = Stone fish biopeptides.

9. Effects on Molecular and Genetics Perspectives (Crispr-Cas9 Delivery)

Mutations instigate most hereditary metabolic syndromes in genes that code for enzymes; enzyme deficiency or inactivity leads to scarcities of the enzyme's product or aggregation of material precursors or metabolites (Groop, 2000). Discovering and treating during the early stages of these syndromes focuses on emergency attention and certainty, improving organ function. Recently, gene editing or therapy has been a hopeful approach for treating challenging diseases, including metabolic syndromes. The fruitful delivery of genes is a perilous step for gene therapy. The utmost updated developed approach of gene editing is CRISPR-Cas9 (Clustered regularly interspaced short palindromic repeats- CRISPR associated 9) technology that, a competent gene-editing implemented according to the anti-viral mechanism controlled by some naturally occurring bacteria (Abdelnour et al., 2021). This technique could allow for the deletion or insertion of a causative genetic component, paving a probability for the whole cure of the syndrome.

Viral delivery is the main gene editing choice and has been widely applied. However, it exhibits some drawbacks, such as replication competence, transduction efficiency, integration, small insert size, inactivation by the accompaniment path, and restricted host range owing to the necessity of cell division for transduction (Kay et al., 2001). Based on the above drawbacks, searching for a biocompatible and safe delivery system is urgently necessary. In this era of biotechnology, numerous nanoparticles encompass lipid-based, glycolipid, inorganic polymers, gold nanoparticles, alginate, and chitosan nanoparticles are expansively used currently for preclinical and clinical investigations (Mout and Rotello, 2017; Abdelnour et al., 2021). Regarding the potential application of chitosan in the delivery system of gene editing, the study of (Saberi et al., 2009) reported that siRNA delivery policy includes polyethylene glycol, chitosan lactate, conjugated with glycyrrhetinic acid and contains the *CRTC2* gene as a target. This CRTC2-siRNA conjugate system effectively silences the CRTC2 gene that regulates hepatic gluconeogenesis in T2DM (Saberi et al., 2009). Jean et al. (2012) researched the silence of DPP-4, an antagonist of incretin, GLP-1 that encourages insulin relief and sustains glucose homeostasis.

The formulated chitosan-DPP-4-siRNA nano-complexes exhibited substantial silence of DPP-4 in cultured situations without seeming cytotoxicity Jean et al. (2012). Moreover, Sharma et al. (2021) developed nano micelles incorporating chitosan that targets adiponectin, conjugated to the oleic acid and adipose homing peptide to ease the delivery of pADN (plasmid adiponectin) to adipocytes. This nano micelle of chitosan (112 nm) is cationic due to the presence of chitosan that shows a protective modulator for genes against enzymatic degradation with a highly encapsulated rate of around 93%. The outcome revealed betterment of insulin sensitivity for up to 6 weeks with single subcutaneous administration of pADN-chitosan-oleic-AHP in *vivo and in vitro* using a diabetic rat model (Banerjee et al., 2020).

Commercial drugs used as anti-inflammatory mediators have numerous side effects and are inappropriate for long-term usage. A research group by Luo et al. (2018) targeted two such factors, e.g., monocyte chemoattractant protein-1 (MCP-1) and tumor necrosis factor-α (TNF-α) that are pro-inflammatory adipocytokines, existing in adipocytes macrophages (ATMs) and adipocytes and lead to knockdown by applied shRNAs against these features. The chitosan nanomicelle/pDNA polyplexes were subcutaneously treated in an obese-diabetic mice model. The outcome showed decreasing levels of numerous classes of pro-inflammatory cytokines such as IL-6 IL-1, TNF-α, and MCP-1, whereas the insulin-sensitizing adipokine, adiponectin levels were augmented. After the literature screening, limited works incorporate CRISPR-Cas9 (Luo et al., 2018; Banerjee et al., 2020; Sharma et al., 2021), nanoparticle-based delivery in treating metabolic syndromes. This strategy is indisputably a commanding policy, as per the recent study and it can proficiently silence the specific causative genes related to some metabolic syndromes. In the upcoming investigations, modulations of the transcriptomics of the causative genes were prepared and potentially applied to the miracle molecules, CRISPR-Cas9, delivered by chitosan nanoformulations.

10. The Potential Challenges of Utilizing Chitosan and its Nanoformulations

According to Yadav et al. (2023), advances in nanotechnology have created nanocomposites based on chitosan with better qualities. These nanocomposites have excellent thermal, mechanical, conductive, and antibacterial qualities. They are efficient in delivering drugs and aid in the healing of wounds. Biomedical sectors hold great promise for chitosan-based nanocomposites, notwithstanding obstacles related to toxicity and in vivo assessments. In vitro testing and fabrication have been the main topics of previous research, but more work is required to address these issues.

According to Kaur et al. (2023), nanoscience and technology were used more and more in targeted drug administration to increase therapeutic efficacy and safety over the previous 20 years. Biodegradable polymers, such as those found in CS drug delivery systems, provide an alternative to controlled drug release through the nose. These carriers represent a new paradigm in medication delivery because of their ability to treat neurodegenerative illnesses. Nasal drug delivery (NDD) is a non-invasive technique that shows great promise for efficiently administering a wide range of pharmaceuticals, including high molecular peptide and protein therapies and low molecular polar chemicals (Weyers et al., 2022). Therefore, the nasal mucosa serves as the main portal through which various therapeutic drugs are directed to specific disease-causing locations that enter the body (Kurono, 2022). As a result, in contrast with parenteral and oral administrations, the nasal cavity's high vascularity expedites regional and systemic pharmaceutical absorption via the nasal mucosa, enabling fast therapeutic action (Chavda et al., 2022).

Additionally, its ability to get past the hepatic first-pass metabolism and blood-brain barrier (BBB) is another important benefit (Nojoki et al., 2022; Khatri et al., 2023). Because of this, lower pharmaceutical doses may be needed to produce more beneficial effects with fewer negative effects.

By necrotic biofilm construction, decreasing its significant components, and preventing microbial proliferation, El-Naggar et al. (2023) suggested that the encouraging findings of the research study in biofilm inhibition motivate usage as a natural, safe, and biocompatible anti-adherent covering in antibiofouling membranes, medical bandages/tissues, and packaging for food. According to Virmani et al. (2023), chitosan and its modified derivatives are employed in pharmaceuticals to produce nanoparticles, medication delivery, and cancer site targeting. These nanoparticles are desirable for many anticancer medications due to their increased potency, efficacy, cytotoxicity, and biocompatibility.

Chitosan is widely used in biotechnology, medicine, and agriculture due to its unique properties. However, its insoluble nature and poor mechanical properties limit its use in biomedical fields. Modifications can increase solubility, creating new derivatives with enhanced properties. Chitosan is also used in wound dressings, speeding up healing and protecting against infection. On the other hand, chitosan, a versatile drug delivery system, has been studied extensively over the past 20 years. However, cytotoxic impacts are still present, and further research is needed to reduce toxicity. Despite numerous studies, there are still few uses for chitosan in the medical field. Further investigation into drug delivery methods, toxicology, and security concerns is crucial.

11. Conclusions

Chitosan is one of the utmost discovered bio-based polymers. According to WHO reports, chitosan is commonly approved and recognized as safe eminence as a food element. Due to its biodegradability and biocompatibility, chitosan has a variety of multifaceted uses, with a distinctive prominence on therapeutic uses and drug delivery schemes. Moreover, the new form of chitosan nanoparticles or chitosan alone has numerous proposes in non-parenteral drug management for metabolic syndromes such as insulin resistance, obesity, diabetes mellitus, dyslipidemia, hyperglycemia, and hypertension due to their physical structures and absence of toxicity. In addition, chitosan nanoparticles have been considered in the pitch of nanomedicine for the formation of novel therapeutic drug schemes due to their enhancement of the bioavailability of drugs and their inferior toxicity, sensitivity, and specificity. Recently, the chitosan nanoparticle-based delivery of CRISPR-Cas9 has been applied in treating metabolic syndromes. Furthermore, the wide range of chitosan NPs has revealed therapeutic likely in various metabolic syndromes.

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