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REVIEW ARTICLE

Chitosan-derived Nanocomposites as Emerging Antidiabetic Therapeutic Platforms

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Abstract

Diabetes mellitus is one of the leading causes of death worldwide. New treatment approaches are necessary regarding traditional oral medication for hypoglycemic control and insulin administration. Chitosan (CS), a natural polymer derived from chitin, has a unique blend of qualities that make it a better choice for use in nanomedical applications, such as its capability of increasing epithelial permeability, biocompatibility, biodegradability, and mucoadhesion activity. Recent developments in CS-derived nanocomposites in drug design act as next-generation platforms for antidiabetic therapy. CS-based nanocomposites can encapsulate insulin, plant-derived bioactives, and peptide analogs by shielding them from enzymatic destruction and allowing controlled release. By addressing the multifactorial components of diabetes, such as oxidative stress and pancreatic β-cell dysfunction, functionalization with targeted ligands or co-loading with antioxidant and anti-inflammatory drugs further improves treatment efficacy. Pre-clinical data show that eco-friendly synthesis methods such as ionic gelation, phytochemical-mediated reduction, and enzymatic cross-linking increase sensitivity to insulin, increase tissue protection, and improve glycemic control. This review highlights the potential of CS-derived nanocomposites as new antidiabetic treatment platforms.

Key words: Chitosan, diabetes, drug delivery, eco-friendly synthesis, nanocomposites, oral insulin, therapeutic platforms

INTRODUCTION

Diabetes mellitus is one of the most significant global health challenges in the 21st century. A growing range of disorders includes microvascular and macrovascular consequences (retinopathy, cardiomyopathy, nephropathy, and neuropathy). According to the International Diabetes Federation, the primary causes of diabetes worldwide are population aging, lifestyle, dietary transition, and urbanization. Imbalanced insulin metabolism leads to substantial alterations in the biochemical function of carbohydrates. Despite advances in pharmacotherapy and existing antidiabetic medications, including alpha-glucosidase inhibitors (acarbose and miglitol), sodium-glucose cotransporter-2 inhibitors (canagliflozin, dapagliflozin, empagliflozin), non-sulfonylureas (metformin), and insulin, these face limitations due to poor bioavailability, systemic side effects, frequent dosing requirements, and variable patient compliance.[1]

The innovative approach of using nanomedicine in anticancer, antidiabetic, and antimicrobial activity has gained significant interest. The synthesis of innovative chitosan (CS)-based nanocomposites to overcome diabetes

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by inhibiting α-glucosidase and α-amylase plays a pivotal role in glucose metabolism by reducing β-cell dysfunction. Water-soluble natural polymers are preferred over polymers that dissolve in organic/inorganic solvents due to wider biomedical applications and biological characteristics. The first naturally extracted chitin was from mushrooms by Henri Braconnot in 1811. CS is a polysaccharide and a chemical derivative of chitin. Nowadays, scientists have isolated CS from different invertebrates such as mollusks, crabs, crayfish, prawns, shrimps, lobsters, and crayfish.[2] The most abundant source of chitin was seen in the shells of crabs and shrimps. The presence of both glucosamine and acetyl glucosamine groups in CS is considered a heteropolymer.

The study reveals that the use of CS-based nanomaterials can easily interact with the negatively and positively charged plasma membrane of bacteria and the glucosamine amino group, respectively. Surface modification of metal oxide nanoparticles (NPs) with CS improves the adaptability of the NPs and improves biological characteristics.[3] The current review critically examines the evolving role of CS-derived nanocomposites as antidiabetic platforms, highlighting their structural attributes, mechanistic pathways, therapeutic applications, advantages, challenges, and future directions. Different approaches used to prepare chitosan-based nanocomposites, together with their stabilizing agents and reported applications, are summarized in Table 1.

ANTIDIABETIC MECHANISM OF CS-BASED NANOCOMPOSITE

The insulin signaling route and phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT) pathway play a significant role in antidiabetic activity and glucose metabolism. The CS-based derivative activates the PI3K/AKT cascade, affects it prominently, and helps regulate glucose uptake in muscle and adipose tissues, lowers blood glucose levels, and improves insulin sensitivity.[9] CS and its oligosaccharides accelerate glucose transporter (GLUT) expression, such as GLUT-2, by stimulating glucose insulin, enhancing proliferation of pancreatic β-cells, and amplifying insulin's effect throughout the insulin-responsive tissues. Furthermore, CS derivatives promote activation of peroxisome proliferator-activated receptor (PPAR-γ) pathways in adipose tissue, which improves glucose and lipid metabolism, increasing adiponectin expression and further sensitization of cells to insulin.[10] CS and its derivative enhance paracellular glucose uptake by modulating PI3K/AKT and ERK signaling, which results in tight junction integrity in intestinal epithelial cells. In a diabetic model, it normalizes blood glucose by reducing insulin resistance and hepatic gluconeogenesis, where it targets the insulin signaling axis and related pathways.[11] The principal pathways through which chitosan-based nanocomposites may influence glucose uptake, insulin signaling, and tissue-specific metabolic responses are summarized schematically in Figure 1.

Silver (Ag)/CS/ascorbic acid nanocomposite

Research studies suggest that the streptozotocin-induced diabetic rat model shows significant antidiabetic potential when injected with Ag/CS/ascorbic nanocomposite.[12] Due to the synergistic effect of each NPs used, it acts as a promising multifunctional agent for diabetic management. Oral delivery of these Ag/CS/ascorbic nanocomposites in diabetic rats remediates hyperglycemia, elevates insulin production, and reduces diabetic nephropathy and liver damage through combined antioxidant, anti-inflammatory, and other regenerative pathways.[13] Also, the combined NPs show dual therapeutic effects targeting hyperglycemia and diabetic complexity.[14]

Fungal CS/Ag nanocomposite

CS/Ag nanocomposites sourced from fungi have been identified as valuable nanomaterials in the realms of healthcare and food production owing to their properties, which combine biodegradable and biocompatible CS of fungal origin with potentially useful functionalities afforded by AgNPs. CS derived from fungi serves as an eco-friendlier polymeric matrix suitable for stabilizing AgNPs, governing their distribution and release, and curbing NP clumping.[15] This explains the promising antimicrobial, antioxidant, and potential antidiabetic properties of nanocomposites based on CS. These antidiabetic effects can emanate from the inhibition of carbohydrate-digesting enzymes, as well as the decrease in oxidative stress rates and contribution to bioactive compound delivery. However, it is necessary to investigate how the concentration of Ag, size of NPs, molecular characteristics of CS, and the conditions of synthesis influence the toxicity and efficacy of these biocomposites.[16]

CYTOCOMPATIBLE CHITOSAN SCHIFF BASE DERIVATIVE

A newly designed cytocompatible CS Schiff base derivative has been fabricated by conjugating CS with particular bioactive chemicals such as sulfonamide derivatives and quinoline-associated aldehydes. The resulting compounds exhibit significant multifunctional bioactivities, including antibacterial, antidiabetic, and anticancer effects. The antioxidant potential of these CS-based derivatives has numerous advantages for diabetic treatment. It emphasizes both −OH and $-NH_2$ groups, which exert robust antioxidant action and also scavenge free radicals, protecting pancreatic β-cells from oxidative damage.[17] It has been reported that ABTS radical scavenging activity up to 59% is seen in the newly formed CS derivative compared to 13% for unmodified CS. The modified CS-based derivative showed promising results in depletion of postprandial hyperglycemia and β-cell impairment. These derivatives activate glucose uptake in hepatic (hepatocellular carcinoma 2 [HepG-2])

and yeast cells in a dose-dependent manner, significantly improving cellular glucose utilization compared to native CS. Enhanced inhibition of key enzymes such as α-amylase and α-glucosidase, which are integral to the breakdown of carbohydrates, helps in controlling blood sugar. Studies have shown near-maximal inhibitory values of 99.78% and 92.10% for α-amylase and α-glucosidase, respectively. For instance, CS-quinoline Schiff base derivatives have shown up to a 54.29% increase in glucose uptake in HepG-2 cells at optimal concentrations. Research demonstrates that these compounds are safe for biomedical applications, exhibiting no major toxicity to normal human cells and being appropriate for advanced therapeutic usage.[18]

CS-loaded p-Coumaric acid NPs

The CS-loaded p-Coumaric acid NPs improve insulin secretion by reducing hyperglycemic effects and decrease blood glucose levels. Serum creatinine and urea are seen to be reduced in the diabetic model following reduction of oxidative stress in kidney tissue, and histopathological outcomes are improved. The gene expression mechanism involves preventing diabetic nephropathy by upregulation of GLUT-2 and downregulation of kidney injury molecule-1. The versatile approach of combining antimicrobial, antioxidant, anti-inflammatory, and antidiabetic activity for managing diabetes has seen promising therapeutic potential. The synthesis of CS-loaded p-Coumaric acid NPs represents a novel and feasible nanotechnology-based drug delivery system in regulating diabetes.[19]

CS-assisted zinc oxide (ZnO) nanocomposite

The application of eco-friendly synthesis of CS-derived ZnO nanocomposites has gained popularity for various applications due to their multifunctional benefits. CS

Table 1: Green synthesis routes for CS-based nanocomposites

Synthesis method	Reducing/Stabilizing agent	Nanocomposites	Application	References
Biopolymer driven	Cellulose, starch, pectin	CS-TiO_2	Useful in drug delivery, improves stability	[4]
Physical green method	Ultrasonication of plant extract, microwave	CS-Fe_3O_4	Synthesis is faster and has uniform morphology	[5]
Plant-mediated	Phytochemicals	CS with different nanoparticles such as Ag, Zn, ZnO	Useful in antidiabetic applications, wound healing, anticancer	[6]
Algae-assisted	Metabolites of Marine algae	CS-CuO	Photocatalytic, Eco-friendly	[7]
Microbial-assisted	Bacteria and fungi	CS-ZnO	Biocompatible, antibacterial, antifungal	[8]

TiO_2: Titanium dioxide, Fe_3O_4: Iron (II, III) oxide, CuO: Copper oxide, Zn: Zinc, ZnO: Zinc oxide, CS: Chitosan, Ag: Silver

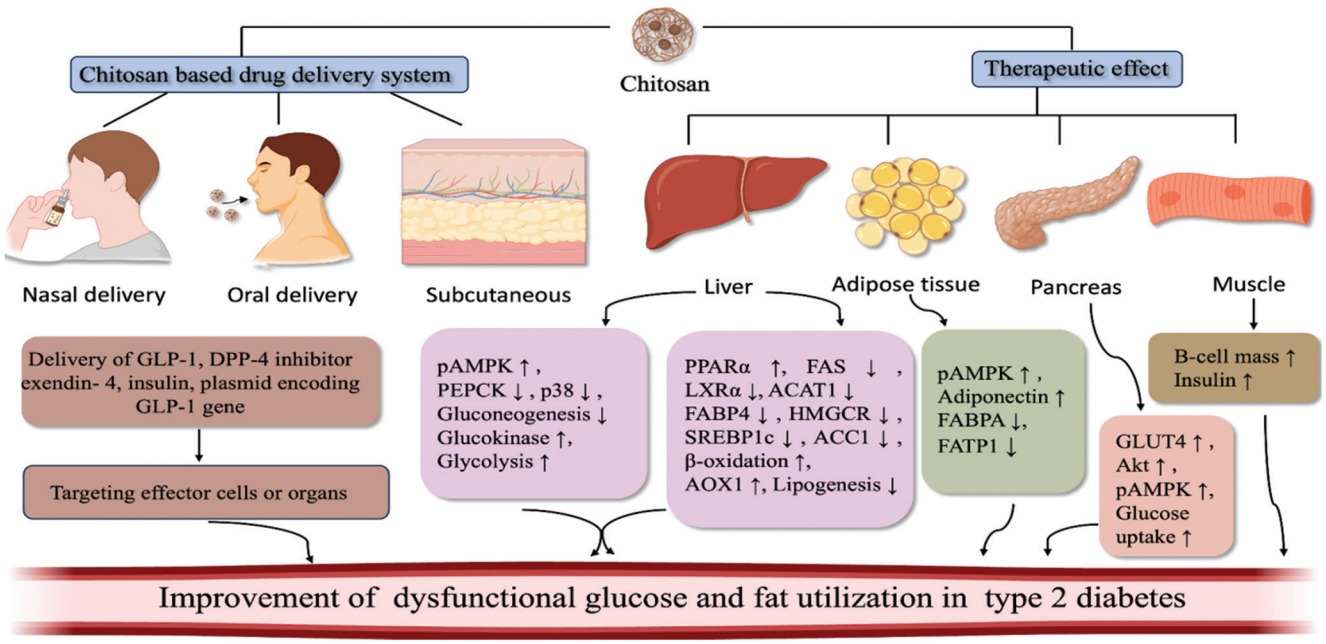


Figure 1: Schematic representation of the antidiabetic mechanisms of chitosan-based nanocomposites

is known for being a biodegradable and biocompatible polymeric material, which helps in stabilizing ZnO NPs and limiting their aggregation in order to allow controlled release and stronger interaction with biological tissues. ZnO may enhance the biological activity of the material through its own reactivity and antioxidant as well as antimicrobial properties. The application of CS/ZnO nanocomposites for antidiabetic purposes may also aid in inhibiting α-amylase and α-glucosidase, reducing oxidative stress, optimizing glucose metabolism, and drug delivery. Their physicochemical parameters may also play a significant role in the final biological efficiency. Nevertheless, potential cytotoxicity induced by ZnO, dose-dependent oxidative influence, stability of NPs, and long-term safety issues must be addressed.[20]

Iron oxide (FeO)/titanium dioxide (TiO_2) fabricated CS/polyvinyl alcohol (PVA) nanocomposite sponge

The diabetic wound healing potential of FeO-fabricated CS/PVA has shown promising results *in vitro* and preliminary evaluation. However, *in vivo* studies are recommended to study the process in detail. *In vitro* assays show promising results, as TiO_2 shows uniform dispersion within the polymer matrix, has excellent hydrophilic and mechanical properties, shows antibacterial and antioxidant activity, shows a high wound closure rate, and is biologically compatible with human skin fibroblast cells. 92.3% wound closure was seen in CPT3 film within 48 h when this combined nanocomposite was incorporated.[21] Furthermore, this nanocomposite shows promising results in diabetic wound models (such as streptozotocin-induced diabetic rats or mice) through various means such as reducing inflammation, providing antimicrobial protection, and enhancing cell proliferation; due to its porous structure and bioactive properties, it supports a favorable healing environment in the models used compared to controls. In chronic diabetic wound healing, the nanocomposite scaffolds or gels inhibit bacterial colonization by maintaining a moist wound environment. Histopathological analyses confirm that the use of TiO_2 nanocomposite shows effective results in wound infection by increasing keratinization, neovascularization, and granulation tissue formation and reducing inflammatory cells.

LUPEOL-CS NPs INFUSED CELLULOSE ACETATE MEMBRANES FOR ENHANCED ANTIDIABETIC ACTIVITY

The action of Lupeol-CS NP has an active antidiabetic mechanism at molecular and cellular levels. Lupeol mainly slows down carbohydrate digestion and reduces postprandial blood glucose levels by inhibiting α-amylase and α-glucosidase enzymes, which contributes to better glucose control. Lupeol helps in regeneration and preservation of pancreatic insulin-producing β-cells by reducing oxidative stress and lipid peroxidation. Lupeol also acts as a potent antioxidant for reducing inflammation by downregulating pro-inflammatory cytokines such as interleukin-6 and tumor necrosis factor-alpha in adipose tissue. It enhances insulin signaling pathways such as insulin receptor (IR), IR substrate-1, PI3K, and AKT in target tissues. Furthermore, it enhances GLUT4 expression and its translocation. In type 2 diabetes, it restores metabolic balance by activating PPARδ and PPARγ and also by improving lipid metabolism and insulin sensitivity. Lupeol also inhibits negative regulators such as protein tyrosine phosphatase 1B to improve glucose uptake.[22]

AG OXIDE AND CS-BASED NANOCOMPOSITE FOR ANTIDIABETIC ACTIVITY

Ag oxide-CS nanocomposites are potentially effective multifunctional nanoplatforms for creating antidiabetic therapies due to the ability of Ag oxide NPs to exhibit bioactive and antimicrobial properties, plus the advantages of CS being biocompatible, biodegradable, mucoadhesive, and possessing controlled release properties. This type of nanocomposite can improve the stability, dispersion, and bioavailability of drugs, as well as have a surface suitable for functionalization and provide targeted drug delivery. From the point of view of antidiabetic properties, it can be assumed that these nanocomposites can involve inhibition of carbohydrate-hydrolyzing enzymes, reduction of oxidative stress, regulation of inflammatory processes, and enhancement of glucose metabolic processes.

CS-based Ag oxide nanocomposite enhances insulin sensitivity by facilitating glucose uptake into peripheral tissues by lowering blood glucose levels efficiently. Furthermore, these nanocomposites possess antioxidant activity by significantly reducing oxidative stress and improving beta cell function in diabetes management.[23] This nanocomposite reduces the toxicity level, which helps in safer and efficient flow of the nanocomposite to the targeted site. Histopathologically, it has been proven that it gradually regenerates the damaged pancreatic beta cells and also protects the liver tissues, which helps in improving the insulin level for better systemic glycemic control.

LIMITATIONS, CURRENT CHALLENGES, AND FUTURE PROSPECTS

Despite their great potential, CS-based nanocomposites encounter a number of constraints that currently limit their translation into clinical and commercial applications. Differences in the CS molecular weight, degree of deacetylation, purity, source, and physicochemical properties affect the formation, stability, drug release, and biological

activity of the NPs significantly. Moreover, the dissimilarity in formulation techniques and experimental conditions complicates the comparison of the outcomes of the works available in the literature. Many of the claims regarding antidiabetic activity are based on *in vitro* or short-term animal models, while the evidence for long-term effectiveness, biodistribution, metabolism, immunological response, and chronic toxicity is scarce. Moreover, NP agglomeration, instability in physiological conditions, premature drug release, and lack of targeting might also negatively affect their therapeutic efficacy. The action of CS nanocomposites in reference to biological barriers and gastrointestinal conditions might also influence their bioavailability and absorption. The possible cytotoxic and accumulation effects need special concern for multipurpose systems with metals and several bioactive components. Furthermore, large-scale manufacturing, reproducibility, price, sterilization, storage stability, approval by regulatory bodies, and uniform quality control represent major obstacles on the way to practical applications.

CS-based nanocomposites provide a promising platform for developing the next generation of antidiabetic therapies based on their biodegradability, biocompatibility, mucoadhesiveness, and ability to enhance the bioavailability of poorly soluble or unstable compounds. Further research should focus on optimizing the above aspects in order to achieve anticipated pharmacokinetics and pharmacodynamic responses. Functionalization of CS with different targeting ligands, peptides, polysaccharides, and stimuli-responsive components can enable targeted delivery and improvement in the therapeutic index of antidiabetic compounds. Combination with the phytochemicals of plant origin, peptides, probiotics, and existing antidiabetic medications could give rise to multifunctional systems acting at various pathophysiological levels, such as oxidative stress, inflammation, insulin resistance, glucose intake, and pancreatic β-cell dysfunction.[24] Advanced characterization methods, *in silico* modeling, and formulation characterization with the help of artificial intelligence technologies, as well as systems biology principles, would further speed up the development of the necessary formulations. It is worth noting that future studies should go beyond *in vitro* models and include well-designed animal experiments and clinical studies to determine pharmacokinetic patterns, long-term efficiency, safety, and effectiveness of the technology.

CONCLUSION

Nanocomposites based on CS are being viewed as sophisticated platforms for the delivery of antidiabetic drugs. The positive physico-chemical features, biodegradability, and mucoadhesivity of CS open new horizons in overcoming some of the limitations stemming from orthodox antidiabetic formulations. By means of the introduction of proper therapeutic compounds, phytochemicals, peptides, or other bioactive agents, these systems can combat various pathological mechanisms of the process of diabetes, such as hyperglycemia, oxidative stress, inflammation, and insulin resistance. However, it should be noted that the field at present mainly remains in the pre-clinical state, and there are still many gaps in the standardization of the formulation and the number of investigations of its mechanisms, including long-term safety assessment, pharmacokinetic evaluation, and clinical validation.[25] Consequently, future efforts should concentrate on the development of formulations based on mechanistic considerations, improved pharmacokinetics and pharmacodynamics, long-term safety evaluation, capacity scaling, and clinical trials. It is crucial to examine interactions between the properties of CS and therapy results from the perspective of structure–activity relationships. The potential of artificial intelligence to contribute to personalized nanotherapeutics is important, together with computational modeling and omics-based approaches.

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