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Review article

Eco-friendly chitosan-based nanostructures in diabetes mellitus therapy: Promising bioplatforms with versatile therapeutic perspectives

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ABSTRACT

Nature-derived polymers, or biopolymers, are among the most employed materials for the development of nanocarriers. Chitosan (CS) is derived from the acetylation of chitin, and this biopolymer displays features such as biocompatibility, biodegradability, low toxicity, and ease of modification. CS-based nano-scale delivery systems have been demonstrated to be promising carriers for drug and gene delivery, and they can provide site-specific delivery of cargo. Owing to the high biocompatibility of CS-based nanocarriers, they can be used in the future in clinical trials. On the other hand, diabetes mellitus (DM) is a chronic disease that can develop due to a lack of insulin secretion or insulin sensitivity. Recently, CS-based nanocarriers have been extensively applied for DM therapy. Oral delivery of insulin is the most common use of CS nanoparticles in DM therapy, and they improve the pharmacological bioavailability of insulin. Moreover, CS-based nanostructures with mucoadhesive features can improve oral bioavailability of insulin. CS-based hydrogels have been developed for the sustained release of drugs and the treatment of DM complications such as wound healing. Furthermore, CS-based nanoparticles can mediate delivery of phytochemicals and other therapeutic agents in DM therapy, and they are promising compounds for the treatment of DM complications, including nephropathy, neuropathy, and

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cardiovascular diseases, among others. The surface modification of nanostructures with CS can improve their properties in terms of drug delivery and release, biocompatibility, and others, causing high attention to these nanocarriers in DM therapy.

1. Introduction

Diabetes mellitus (DM) has had significant effects and consequences on the lives of people around the world, urging scientists to improve their knowledge of DM pathogenesis and develop new therapies for it (Brito-Casillas et al., 2016). Based on the in silico and in vitro studies, the pathogenesis of DM is considered to be multifactorial, and different interactions are implicated in its progression and pathogenesis (Graham and Schuurman, 2015). The animal model has improved our understanding of DM pathogenesis (Gale, 2005; Roep and Atkinson, 2004), but there is still a chimera about animal replacement (Russell and Burch, 1959). The studies on human, in vitro, and animal models have been interested in understanding the underlying mechanisms involved in DM pathogenesis (Roep and Atkinson, 2004). DM is defined as a metabolic disease in which hyperglycemia occurs and can be caused by insulin deficiency in a direct or indirect way (Bielka et al., 2022). Type I DM (TIDM) and type II DM (TIIDM) are two main kinds of DM in humans. As an autoimmune disease, antibodies are secreted in TIDM patients that are against pancreatic β-cells to mediate pathogenesis of TIDM, which mediates insulin deficiency (Bluestone et al., 2010). On the other hand, insulin resistance can lead to development of TIIDM. Then, enhanced demand for insulin in peripheral tissue occurs, impairing and disrupting the function of beta cells (Udayappan et al., 2014). The management of DM should be performed immediately, and a lack of proper management leads to long-term complications affecting the lives of DM patients. When DM is not controlled, it leads to the development of complications such as retinopathy, chronic kidney disease, neuropathy, cardiomyopathy, and an increase in mortality (Nathan et al., 2013; Stratton et al., 2000; Orchard et al., 2015). In 2019, it was mentioned that the number of people with DM is increasing, and by 2045, the number of DM patients will increase to 700 million from 463 million (Saeedi et al., 2019). The most prevalent type of DM is TIIDM, which can result from oxidative stress and inflammation (Ma et al., 2018). When metabolic disorders occur, oxidative stress is observed, which leads to impaired insulin activity (Dominique, 2002; Fukunaka and Fujitani, 2018) via multiple molecular pathways (Alberici et al., 2011) and the generation of reactive oxygen species (ROS) (Rösen et al., 2001). The production of ROS can result in stresses and damages in β cells that disrupt the release of insulin from cells (Evans, 2003). Moreover, ROS overgeneration can result in activation and upregulation of NF-κB (nuclear factor-κB) and PKC (protein kinase C). These alterations result in insulin-related molecular pathways for mediating insulin resistance development (Scivittaro et al., 2000; Kaneto et al., 2002; Goldin et al., 2006). Another risk factor for development of DM is inflammation (Xie and Du, 2011). Different molecular pathways and kinases are affected by inflammation to induce insulin resistance in DM. The adipocytes and immunocytes are able to secrete pro-inflammatory factors such as IL-6 and TNF-α in DM pathogenesis (Crook, 2004; Monami et al., 2014; Mahmoud and Al-Ozairi, 2013; Winer et al., 2016; Gratas-Delamarche et al., 2014). These cytokines and inflammatory factors lead to upregulation of NF-κB in insulin resistance development (Crook, 2004; Mahmoud and Al-Ozairi, 2013; Winer et al., 2016; Gratas-Delamarche et al., 2014; Donath, 2013). Moreover, when there are high levels of IL-6 and TNF-α, it can cause dysfunction and impairment in β cell function (Donath, 2013). The dysregulation of AMPK signaling has also been implicated in the development of diabetic complications and insulin resistance (Entezari et al., 2022).

Since diabetic complications can decrease life quality of patients, significant effort in understanding their pathogenesis and providing treatment approaches have been provided. The diabetic nephropathy can be alleviated by the function of glabridin that reduces ferroptosis through increasing SOD and GSH levels, and can suppress VEGF/Akt/ERK axis (Tan et al., 2022). The tubular injury in diabetic nephropathy can be reduced by the function of PACS-2 through increasing mitophagosome by binding to BECN1 and also, preventing mitochondrial recruitment of DRP1 (Li et al., 2022a). The podocyte injury is observed during diabetic nephropathy and it has been reported that METTL3 increases apoptosis and inflammation for this purpose (Jiang et al., 2022). Furthermore, when DM occurs in mice, cardiac pyroptosis is a problem that injury in mitochondria and upregulation of cGAS-STING can result in this condition (Yan et al., 2022). The left ventricular remodeling is observed in diabetic cardiomyopathy that down-regulation of ADAM17 alleviates this condition (Xue et al., 2022). The expression level of SIRT3 increases by FGF21 to promote mitochondrial integrity and function in amelioration of diabetic cardiomyopathy (Jin et al., 2022). TRPV1 expression enhances by capsaicin to increase eNOS levels and reducing ROS generation in reducing cardiac injury in DM (Wang et al., 2022a). Furthermore, ferroptosis and inflammation are reduced by 6-gingerol in amelioration of diabetic cardiomyopathy (Wu et al., 2022).

Nanoparticles have obtained much attention in recent years in the treatment of DM and its complications. A recent study has developed thermosensitive hydrogels containing Prussian blue nanoparticles and found that their mechanism of action is unique: by reducing the generation of ROS and improving mitochondrial function, they are able to ameliorate wound healing in DM (Xu et al., 2022). The stimulation of the proteasome pathway can lead to DM development. When gold nanoparticles are used for the treatment of DM, they can lead to a reduction in oxidative stress, inflammation, and glucose levels via inhibiting the function of ubiquitin-proteasome pathway (Al-Shwaheen et al., 2022). Moreover, since copper nanoparticles have antioxidant activity, they may be beneficial in the treatment of DM via decreasing oxidative damage, one of the factors involved in DM pathogenesis (Ameena et al., 2022). The eco-friendly synthesis of nanoparticles has been beneficial in recent years in the treatment of DM. Silver nanostructures can be synthesized from Azadirachta indica kernel aqueous extract, and then they can exert anti-diabetic and anti-inflammatory activities (Lan Chi et al., 2022). Combination therapy has also been beneficial in the treatment of DM. It has been shown that a combination of rutin and selenium nanostructures can result in reduced expression of JAK2/STAT3 and induction of Nrf2 axis in alleviation of diabetic nephropathy (Zaghloul et al., 2022). Moreover, when hydrogels are developed for the purpose of DM therapy, they can contain both therapeutic drugs and nanostructures for the amelioration of DM and its complications (Entezari et al., 2022). The green/bio-synthesized nanostructures have obtained high potential in DM therapy. The silver nanocarriers can be biosynthesized from Cyanobacteria Synechocystis sp with 10–35 nm diameter and spherical shape that possess high wound healing ability in diabetic model and can increase VEGF expression as angiogenic factor (Younis et al., 2022). The topical gels can be embedded in solid lipid nanostructures and are utilized for purpose of fluoxetine repurposing to increase wound healing feature (Fatima et al., 2022). The gold nanostructures can also be synthesized from Eryngium thyrsoideum Boiss Extract that have high anti-inflammatory function through reducing TNF-α and IL-6 levels for DM therapy (Mahmoudi et al., 2022). According to these studies, nanoparticles have obtained much attention in recent years in the treatment of DM, and their conjugation with other compounds or their employment for drug delivery can be beneficial for DM therapy (Table 1) (Gadoa et al., 2022; Lawal et al., 2022; Ul Haq et al., 2022; Ahmed et al., 2022; Venkatesan et al., 2022a). In the current review, a focus is placed on the application of chitosan-based

Table 1
The application of (nano)platforms in DM therapy.

(Nano)platform	Remark	Ref
Silver nanostructures	Green synthesis from the Extremophile Plant Aeonium haworthii Antioxidant, antimicrobial and antidiabetic activities	Essghaier et al. (2022)
Gold nanostructures	Green synthesis from leaf extract of Dittrichia viscosa Decreasing hyperglycemia Reducing hepatic gluconeogenesis	Ayyoub et al. (2022)
Ag and NiO nanostructures	Biosynthesis from VPLE 20–35 nm particle size Hepatoprotective activity in DM	Gao et al. (2020)
Novel glucose-responsive nanoparticles based on p-hydroxyphenethyl anisate and 3-acrylamidophenylboronic acid	Decreasing blood glucose and alleviation of diabetic nephropathy Degradation and slow release of HPA Improving renal function Decreasing inflammation	Ma et al. (2022)
Composite hydrogel containing resveratrol-laden nanoparticles and platelet-derived extracellular vesicles	High biocompatibility Decreasing macrophage iNOS expression Reducing inflammation	Zhu et al. (2022)
Zinc oxide nanostructures	Promoting levels of CD4, CD8, and GLUT-4 and reducing inflammation	Elassy et al. (2020)
Chitosan/alginate nanostructures	Improving wound closure rate	Sheir et al. (2021)
Silver nanostructures	Bio-generation from Eryngium thyrsoideum Boiss Extract and improving liver function in DM	Mahmoudi et al. (2021)
Cerium oxide nanostructures	Antioxidant and anti-apoptotic function in testicular tissue of diabetic rats	Solgi et al. (2021)
Gold nanostructures and MXene composite	Detection of glucose in diabetic tears	Cui et al. (2022)
Metal nanoparticles	Biosynthesis from leaves of Ficus palmata Anti-inflammatory and anti-diabetic functions	Sati et al. (2020)
PLGA nanostructures	Delivery of fenofibrate in alleviation of diabetic retinopathy Preventing retinal dysfunction Decreasing retinal vascular leakage Suppressing retinal leukostasis Reducing levels of VEGF and ICAM-1	Qiu et al. (2019)

nanoparticles in the treatment of DM. Fig. 1 schematically displays DM (see Fig. 2).

2. Chitosan: from environment, chemistry to biological applications

The nano-scale delivery systems opened a new gate in the treatment of diseases, but conventional drug delivery systems still have some drawbacks that should be addressed, such as not being able to deliver the drug to the right place, having low absorption, which can lead to poor bioavailability, and being hard to dissolve (Ertas et al., 2021). When accumulation of drugs in non-specific tissues occurs, it can lead to adverse impacts. The new and smart delivery systems have been developed to reverse the side effects and drawbacks of conventional delivery systems and improve therapeutic and clinical results in patients (Jan et al., 2022). Now, this question may be asked: Why is drug discovery not preferred to nano-scale delivery systems? Overall, the process of drug discovery and introducing new drugs with potential therapeutic effects is time-consuming and expensive, while nanoparticle synthesis and development are simple and affordable. Nanotechnology has opened its way in the treatment of various diseases, and one of the most important applications of nanoparticles is in targeted delivery of drugs and other cargo in cancer therapy (Ashrafizadeh et al., 2022a, 2022b, 2023a). Moreover, biocompatible nanostructures such as exosomes have been introduced recently as promising factors in the treatment of DM (Ashrafizadeh et al., 2022c). Chitosan (CS) is a chitin derivative obtained by removing the acetate portion of chitin (Mohammed et al., 2017). In fact, deacetylation of chitin in presence of heat results in production of CS. CS is defined as a naturally occurring polysaccharide, and it has important features such as a positive charge, a highly basic nature, a mucoadhesive feature, high biocompatibility, and has been approved by the Food and Drug Administration (FDA) for the purpose of tissue engineering and drug delivery. The chitin that is found in nature and the environment is attached to proteins and minerals, and therefore, acidification and alkalinization of chitin lead to generation of CS. Then, when purification of chitin occurs, it is transformed into CS via N-deacetylation method. The modification of this process can lead to some changes in final product in terms of molecular weight and pKa (Sorlier et al., 2001) that can be monitored through regulating deacetylation degree, chitin source, and reaction extent. The non-toxicity and high biocompatibility of CS have been completely interesting for researchers, and structurally, CS has been comprised of randomly distributed β-(1, 4)-linked d-glucosamine (deacetylated) and N-acetyl-d-glucosamine (acetylated) units (Rizeq et al., 2019). Chitin is present in cell walls of fungi, and it can also be found in fish and invertebrates. Due to the presence of hydroxyl and amine groups in the structure of CS, this polymer can be easily modified, and this chemical modification can improve its characteristics. In addition to biocompatibility, one of the most important features of CS is its biodegradability, which means that after degradation by enzymes, it is changed and transformed into oligosaccharides that are again non-toxic and biocompatible, confirming the application of CS in clinics. In biomedicine, CS-based nanostructures have been beneficial for antimicrobial, anticancer, drug delivery and tissue engineering applications (Mohebbi et al., 2019). Moreover, CS-based nanostructures have attracted much attention in the fields of ophthalmology, dentistry, bio-imaging, bio--sensing, and diagnosis (Conti et al., 2000).

Notably, chemical modification of CS is advantageous in improving its physical and chemical properties, and moreover, it can expand the application range of CS derivatives (Wang et al., 2020a). The purpose of chemical modification of CS is to greatly improve its properties in the treatment of diseases, including biocompatibility, bioactivity, and biodegradability, while their antibacterial, anticancer, antiviral, and other activities are sustained (Christou et al., 2019; Iftime et al., 2019; Kaczmarek et al., 2019; Kritchenkov et al., 2019; Lin et al., 2018; Pavoni et al., 2019). Currently, CS derivatives have been fabricated as nanoparticles, hydrogels, microspheres, and micelles. CS-based derivatives are beneficial for purposes of drug delivery and as adjuvants in the development of vaccines (Caracciolo et al., 2019; Cheah et al., 2019; Islam et al., 2019; Leso et al., 2019; Nguyen et al., 2019; Sah et al., 2019; Zhang et al., 2019). The chemistry of CS modification is important. Briefly, there are C3–OH, C6–OH, C2–NH2, and acetyl amino and glycoside bonds on the surface of CS that are known as functional groups (Razmi et al., 2019). Among these functional groups, the acetyl amino and glycosidic bonds are stable, and their fracture is not easy. C3–OH is considered a secondary hydroxyl bond that cannot undergo rotation freely, and due to its steric hindrance, it does not undergo reaction easily. Both C6–OH and C2–NH2 can undergo chemical modification via different types of molecular design. The chemical modification of CS significantly improves its applications (Braz et al., 2020; Medeiros

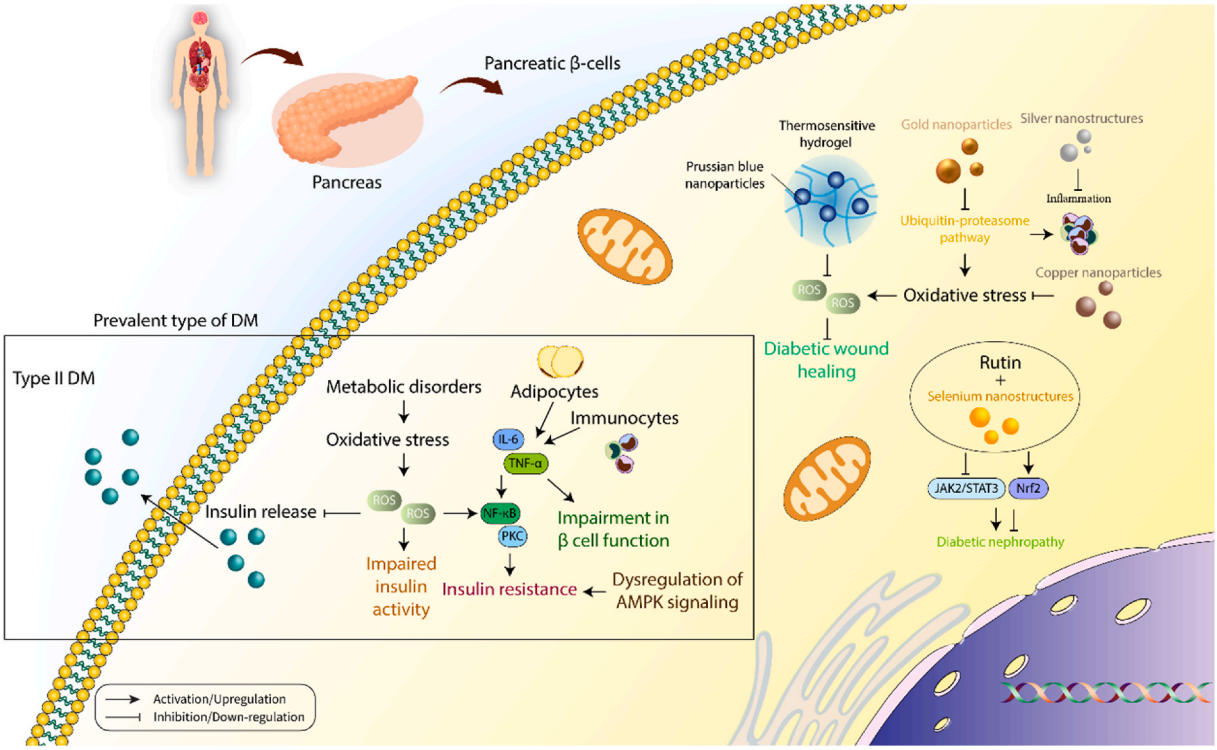

Fig. 1. A schematic representation of DM.

Borsagli et al., 2018; Wang et al., 2016). Recently, studies have focused on the biomedical applications of CS and its derivatives, their biological significance, and their importance in the treatment of diseases (Abd El-Hack et al., 2020; Zhao et al., 2018).

CS-based nanostructures can be used for gene delivery. Due to the positive charge of CS, it can form stable complexes with genes that have a negative charge, and after specific delivery, much improvement in the treatment of human diseases, especially cancer, can be provided (Ashrafizadeh et al., 2021). Moreover, drug resistance is one of the challenging conditions in treatment of cancer. This condition comes from lack of specific delivery of drugs into tumor cells, while their encapsulation by CS-based nanostructures improves their internalization in cancer cells and prevents the emergence of drug resistance (Ashrafizadeh et al., 2020, 2023b). The function of CS-based nanoparticles is more than their simple application in cancer therapy, and it has been shown that application of these nanostructures leads to the development of biocompatible scaffolds for purpose of wound healing (Abadehie et al., 2021). The biomedical application of CS-based nanoparticles is too vast. The development of smart CS-based nanoparticles leads to their exerting anti-oxidant and anti-inflammatory functions in reducing levels of cytokines and pro-inflammatory factors that are beneficial in treatment of apical periodontitis (Hussein and Kishen, 2022). The CS-based nanoarchitectures can be used for targeted delivery of isolongifolene that mediates sustained release of drugs in cancer therapy (Manimaran et al., 2022). However, one of the most important applications of CS is in the antimicrobial field, and it has been shown that coating polymeric silver and gold nanostructures with CS leads to high antibacterial activity (Huq et al., 2022). When selenium nanostructures are coated with CS, their inhibitory impact on PRRSV replication is enhanced, and by increasing ROS generation, they induce JNK pathway to mediate apoptosis (Shao et al., 2022). Octominin, as an antimicrobial peptide, can be loaded into CS-based nanoparticles, and such drug-loaded nanostructures are beneficial in exerting antibacterial and antifungal activities (Fig. 1) (Jayathilaka et al., 2022). The next sections focus on the role of CS-based nanoparticles in treatment of DM.

3. Biomedical application of CS-based nanoplatforms: A summary

The CS-based nanoplatforms are extensively utilized in treatment of various diseases. Before discussing the potential of these nanoparticles in DM therapy, it is better to provide a summary of their use in treatment of diseases. The pharmaceutical industry has been evolved by CS-based nanostructures and their most application is development of safe and biodegradable nanocarriers with various biomedical applications from antimicrobial to cancer therapy and development of vaccines (Khalaf et al., 2023). The natural products can be delivered by CS-based nanostructures in treatment of human diseases. Curcumin is a bioactive compound of *Curcuma longa* and one of its problems is low bioavailability that foxtail millet prolamin/caseinate/CS hydrochloride composite nanostructures improve its stability and retention (Chen et al., 2023). The alginate/CS nanostructures can deliver quercetin increasing its antibacterial activity with high antioxidant activity (Nalini et al., 2022). The CS nanostructures have high entrapment efficiency for quercetin up to 83.65% and their antibacterial activity is high (Zhou et al., 2022a). Because of their remarkable antibacterial activity, quercetin-loaded CS nanostructures have been developed for regulating bacterial adhesion to urethral catheter (Messias de Souza et al., 2022). The antibacterial compounds such as ε-poly-lysine-epigallocatechin gallate can be loaded in sodium alginate/CS nanostructures in improving their activity (Li et al., 2022b). Furthermore, CS-based nanoplatforms are promising factors for development of vaccines and improving function of immune system (Gao et al., 2022). The thermosensitive nanoarchitectures can be fabricated from CS to promote delivery of doxorubicin in cancer chemotherapy and by simultaneous delivery of indocyanine green (ICG), they induce phototherapy in increasing tumor suppression (Zhang et al., 2022a). One of the problems in cancer therapy is lack of specificity of anti-tumor compounds that CS-based nanoparticles can mediate prolonged release of drugs in tumor suppression (Alhodieb et al., 2022). The CS-hybrid nanostructures can be functionalized with cinnamaldehyde to deliver doxorubicin in triggering apoptosis, increasing ROS production, promoting caspase

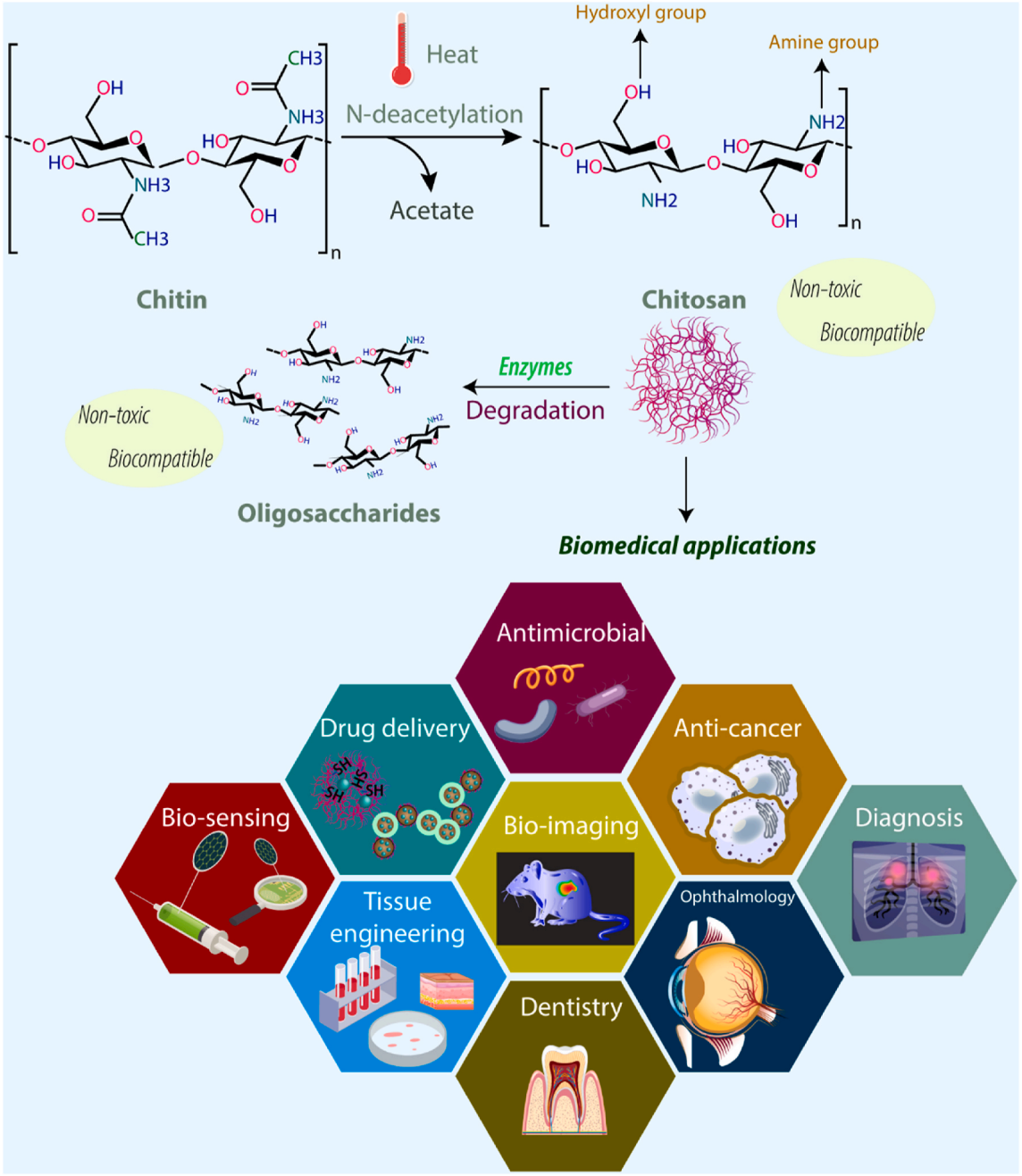

Fig. 2. An overview of CS and its biomedical applications.

expression and mediating mitochondrial dysfunction (Zhou et al., 2022b). For treatment of hepatocellular carcinoma, silica nanostructures have been functionalized with chitosan and cancer cells membrane and although CS-based nanostructures have not been used, this study demonstrates that even functionalization of nanoparticles with CS is beneficial in improving their anti-cancer potential, while minimizing toxicity on normal cells (Espinoza et al., 2023). When Wistar rats are exposed to carbon tetrachloride, nephrotoxicity is mediated that CS nanostructures alleviate this condition (Nomier et al., 2022). CS-based nanoparticles have shown high stability in simulated digestion condition (Li et al., 2022c) and they can be used for delivery of genetic materials such as miRNA (Sun et al., 2022).

4. Chitosan-based nanostructures and insulin delivery

The protein/polymer complexes are used for protein delivery, since they can protect against degradation (Pagels and R.K. Prud'homme, 2015) and increase penetration through biological barriers (Sharma et al., 2015). Moreover, such nanostructures can guide proteins to specific targets (Amidi et al., 2010). However, using globular proteins for production of nanostructures does not lead to generation of stable nanostructures due to salt shielding of electrostatic interaction between protein and polymer (Zhu et al., 2014). The stability of protein-polymer complexes can be significantly improved by adding hydrophobic interactions and hydrogen bonding (Zhu et al., 2014). In order to conjugate hydrophobic molecules to polymers, random conjugation is performed (Guo et al., 2008). In an experiment, CS nanostructures have been prepared for insulin delivery, and their modification with fatty

acids and quaternary ammonium has been conducted. The nanostructures demonstrated a particle size of 280 nm, and they were produced as a result of electrostatic and hydrophobic interactions among CS and insulin. The entrapment efficiency was more than 98%, and fatty acid modification promoted hydrophobicity of nanostructures. When the hydrophobicity of nanostructures increases, their cellular uptake in hepatocytes enhances, and their antidiabetic activity is suggested to be higher. Moreover, CS nanoparticles significantly improved bioavailability of insulin by 233% and 311%, upon modification with lauric acid and oleic acid, respectively (Li et al., 2018). Oral delivery of insulin is considered a promising way to treat DM due to the ease of administration. Moreover, insulin oral delivery can provide physiological release of this agent, improve homeostasis of glucose in body and reduce the problems related to frequent administration and injection of insulin (Zambanini et al., 1999). However, poor absorption of insulin impairs its bioavailability, which results from its high molecular weight, the presence of an acidic environment, and the chance of degradation by enzymes in stomach (Shan et al., 2015; Li et al., 2017). Therefore, oral delivery of insulin, especially by CS-based nanoparticles, has been followed. A recent experiment has developed mucoadhesive nanostructures based on mucin-CS complex for oral delivery of insulin, and they had particle sizes of 479.6 and 504.1 nm with zeta potentials of 22.1–31.2 mV. The entrapment efficiency for insulin is different; it can be high (up to 92.5%), and it mediates controlled release for 8 h. In vivo experiments also revealed that oral administration of insulin via such nanostructures promotes its ability to reduce glucose levels when compared to insulin alone (Mumuni et al., 2020). CS is one of the most biocompatible and common polymers in drug delivery. It appears that modification of CS can increase its potential in delivery, such as thiolated CS that has thiol groups that can be immobilized on amine groups, and such modification also improves mucoadhesive features. When it adheres to mucus, it increases the time of insulin release in gut (Bravo-Osuna et al., 2007). A recent experiment has highlighted that thiolated CS nanostructures have a capacity for insulin delivery with a particle size of 220 ± 4 nm and mediate prolonged release of insulin at a pH level of 5.3. According to in vivo results, the viability of cells did not change upon exposure to these nanostructures, and they can attach to the tip of the microvilli. The levels of insulin and glucose changed upon administration of CS nanostructures, and they improved biodistribution of insulin, which is important in DM therapy (Sudhakar et al., 2020).

Insulin is a large protein with such a hydrophilic nature that it is not possible to directly load it into CS-lecithin nanostructures. The lipophilicity of insulin can be changed upon chemical alteration or physical conjugation to phospholipids, and such a strategy can improve permeability through mucus and enhance stability against enzymatic degradation (Peng et al., 2010). Since chemical modification of large proteins can change their structure, it is recommended to use insulin-phospholipid complexes. In an experiment, lecithin/CS nanostructures were developed that can self-assemble into nanocarriers with a size of 180 nm and an entrapment efficiency of 94%. They have a loading efficiency of 4.5% for insulin, and they have a hollow core with different bilayers. The administration of insulin-loaded nanostructures into an animal model led to improvements in glycemic profile and enhanced pharmacological availability of insulin up to 6.01% (Liu et al., 2016). One of the complications of DM is delayed blood flow, particularly in venules. When the blood circulation reduces, the presence of granular or massive red blood cells is obvious in the microcirculation, and sometimes it can cause interruption of blood flow. Simultaneously, white blood cells can adhere to the walls of blood vessels. Moreover, the expression level of VCAM-1 increases on the surface of microvascular endothelial cells (Xu et al., 2018a). When leukocytes are stimulated and adhere, the generation of free radicals is enhanced, which can result in damage to local vascular endothelial cells and mediate damage and injury to tissues (Taniyama and Griendling, 2003). Chitosan-microcapsulated insulin is able to ameliorate mesenteric microcirculation dysfunction in diabetic rats, and for this purpose, it downregulates the expression levels of COX-2 and VCAM-1 (Xu et al., 2018a).

Table 2
The use of CS-based nanoparticles for insulin delivery.

Nanovehicle	Remark	Ref
Poly (lactic-*co*-glycolic acid) and chitosan composite nanocarriers	Using electrostatic self-assembly for preparation of nanostructures Good hypoglycemic feature in vivo Oral delivery of insulin	Xu et al. (2017)
Insulin-chitosan complex	Nanolayer encapsulation of CS-insulin complex with entrapment efficiency of 90% Increased solubility Reducing blood glucose levels	Song et al. (2014)
Insulin-loaded trimethyl chitosan nanoparticles	Upregulation of IGF1 and IGF2 in the hippocampus of diabetic rats	Kalantarian et al. (2019)
Gold nanoparticles onto chitosan functionalized PLGA nanoparticles	Particle size of 138 ± 23, 16 ± 2.2, and 50 ± 9.3 nm High insulin retention Decreasing blood glucose levels	Asal et al. (2022)
PLGA nanoparticles coated with 5 β-cholanic acid conjugated glycol chitosan	Long-term release, increasing blood circulation time and reducing glucose levels in blood	Wang et al. (2021a)
Dual chitosan/albumin-coated alginate/dextran sulfate nanoparticles	Preventing 70% of insulin release in stomach High permeability of insulin across cells Using clathrin-mediated endocytosis	Lopes et al. (2016)
Chitosan-modified porous silicon microparticles	Elevating the permeability of insulin across intestinal cell layers	Shrestha et al. (2014)
Chitosan nanoparticles	Particle size less than 45 nm, narrow size distribution and high encapsulation efficiency up to 90% pH-sensitive release of insulin	He et al. (2017)
Chitosan-coated solid lipid nanoparticles	Promoting oral absorption of insulin	Fonte et al. (2011)
Boronic Acid-Conjugated Chitosan Nanoparticles	Providing controlled release of insulin	Siddiqui et al. (2016)
Polymeric nanoparticles based on carboxymethyl chitosan in combination with painless microneedle therapy systems	Increasing transdermal delivery of insulin	Zhang et al. (2020)
Insulin-loaded chitosan-alginate nanoparticles	Decreasing urea, uric acid and creatinine levels, and promoting antioxidant activity	Heidarisasan et al. (2018)
Alginate Calcium Microbeads Containing Chitosan Nanoparticles	Reducing blood glucose levels in a time interval of 96 h	Li et al. (2021a)
Carboxymethyl-β-cyclodextrin-grafted chitosan nanoparticles	Improving oral delivery of insulin and increasing ability in reducing blood glucose levels	Song et al. (2018)

Arabic gum is one of the biocompatible and biodegradable polymers, which can be used for oral and topical delivery as a suspending and emulsifying agent (Bhardwaj et al., 2000). Moreover, it can be used as a bioadhesive compound (Bhardwaj et al., 2000). The ionic gelation method was utilized for the preparation of nanostructures from CS and Arabic gum to mediate delivery of insulin. Cargo release occurred at an acidic pH, and due to enhanced solubility of CS at such a pH level and the high swelling of Arabic gum at pH levels greater than 6.5, the release of insulin at a pH level of 6.5 was reduced. Therefore, they are promising nanoparticles for insulin delivery (Avadi et al., 2010). Moreover, alginate–CS–PEGylated nanostructures release insulin in response to glucose levels for DM therapy (Najafikhah et al., 2018). Therefore,

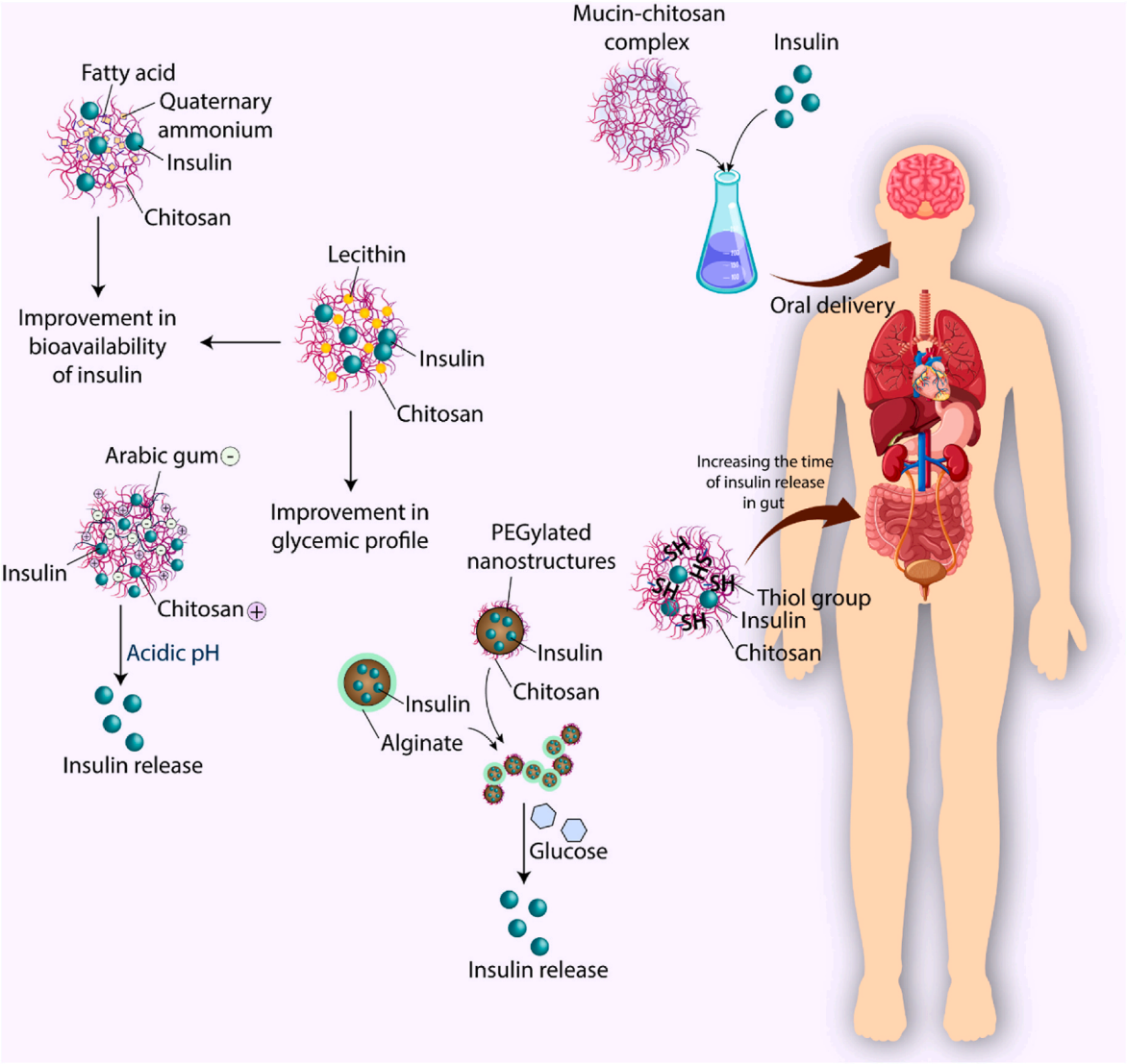

Fig. 3. The use of CS-based nanoparticles for insulin delivery.

accumulating data shows that CS-based nanostructures can provide insulin delivery that may pave the way for future applications in DM therapy (Table 2 and Fig. 3) (Shaaban et al., 2022; Ghavimishamekh et al., 2019; Kalantarian et al., 2018; Tsai et al., 2019; Du et al., 2023).

5. Chitosan-based hydrogel in diabetes mellitus therapy

Hydrogels are networks of hydrophilic polymers that can hold a lot of water and can swell and shrink. Due to their porosity and low toxicity, hydrogels can be used to make drug delivery systems that are biocompatible and allow for controlled drug release. Hydrogels have obtained much attention in biomedicine, and the highest amount of hydrogel is produced in the USA (Narayanaswamy and Torchilin, 2019). One of the complications of DM is chronic wounds, which are clinically important and decrease the quality of life of patients. Chronic wounds in DM can lead to repeated amputations of peripheral limbs, and such wounds either display resistance to clinically employed drugs or the healing process is slow (Zhou et al., 2011). The aim of wound healing as a natural process is to recover the integrity of skin through proliferation and regeneration of skin tissue. In wound healing, a number of processes are involved that may overlap, including hemostasis, inflammation, angiogenesis, fibroblast proliferation, and tissue remodeling (Ayello and Cuddigan, 2004). Different cells and matrices work jointly during wound healing to increase and restore the integrity of skin (Eming et al., 2014). An experiment has developed CS-PEG hydrogels for prolonged release of silver nanostructures, and compared to bare CS-PEG hydrogels, the nanoparticle-loaded hydrogels display higher porosity, swelling degree, and WVTR. Moreover, silver nanoparticle-loaded CS hydrogels have superior antioxidant and antimicrobial activities, and they accelerate process of wound healing. The silver nanostructures are released from hydrogel in a time interval of seven days, which is important for wound healing (Masood et al., 2019). On the other hand, exosomes are small vesicular bodies that can be originated from many cells, and they are considered natural and endogenous nanostructures with a size of 30–150 nm. Exosomes facilitate process of cell-cell communication that is important for tissue repair and regeneration, disease therapy, and others (Kourembanas, 2015; Rani and Ritter, 2016; Tkach and Théry, 2016). Exosomes are intracellular platforms that can mediate transfer of lipids, proteins, RNAs, and other bioactive molecules (Raposo and Stoorvogel, 2013). The exosome-derived mesenchymal stem cells have been shown to accelerate process of wound healing and skin regeneration. Exosomes can increase angiogenesis, growth, migration, and re-epithelization in improving wound healing. Therefore, exosomes can be considered as promising alternatives to stem cells for disease therapy (Kourembanas, 2015; Zhang et al., 2015; Li et al., 2016; Phinney and Pittenger, 2017). The exosomes isolated from

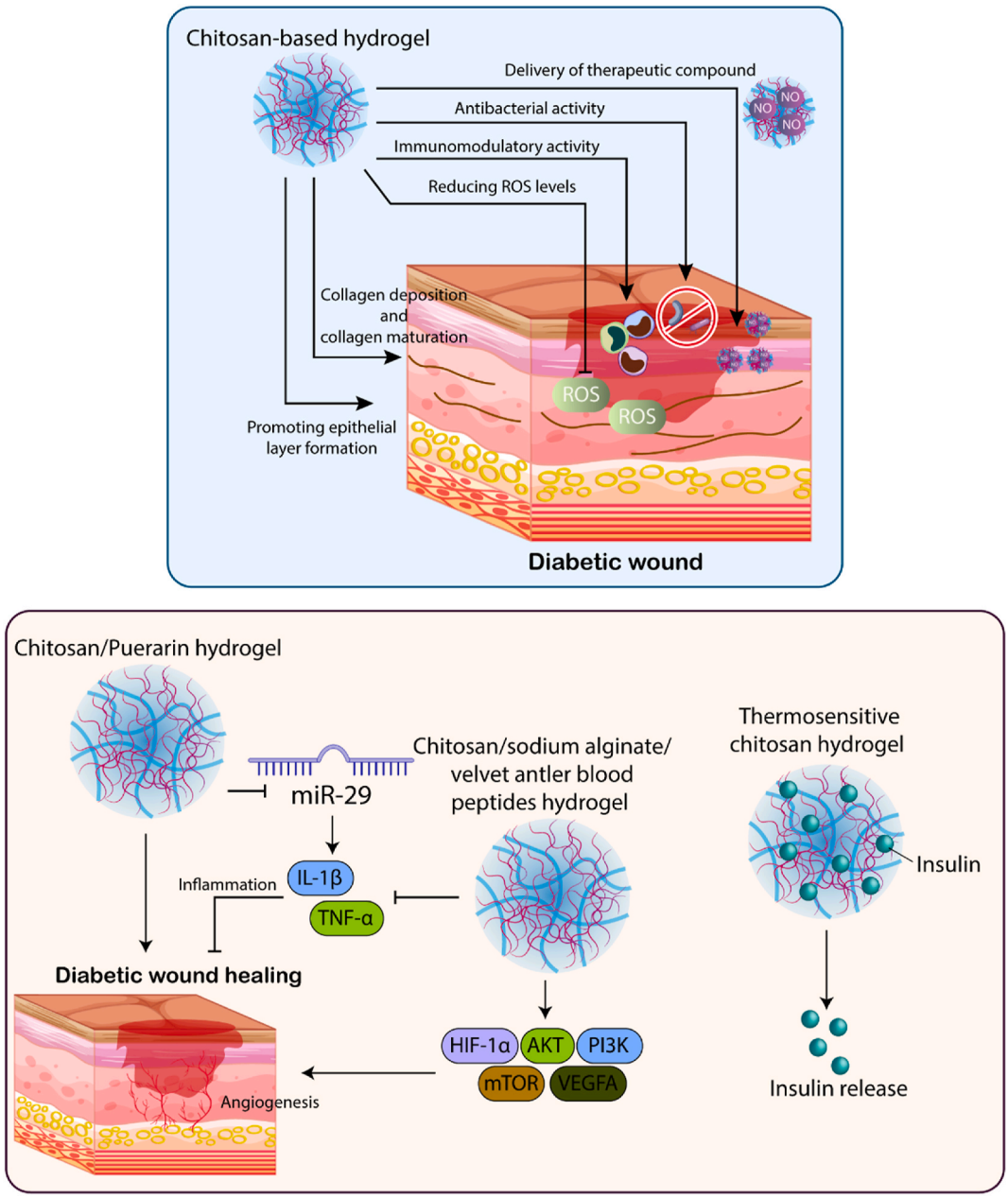

Fig. 4. The application of CS-based hydrogels in DM therapy.

mesenchymal stem cells have a particle size of 127 nm, and on the other hand, CS/silk hydrogel shows appropriate swelling and moisture retention ability. Loading exosomes in hydrogels is promising in improving ability in wound healing. The application of exosomes or hydrogels leads to re-epithelialization and collagen production, and it accelerates wound healing process (Shi et al., 2017).

The compounds and drugs in traditional Chinese medicine have been suggested to have immunomodulatory functions (Wang et al., 2021a; Casey et al., 2015; Zhang and Wei, 2020). Puerarin (PUE) is a natural compound that can be found in the root of the kudzu vine, and it has important actions, including cardioprotective, neuroprotective, and glucose-lowering effects (Chen et al., 2018a, 2018b; Meresman et al., 2021). The wound healing effect of PUE has been confirmed in various studies (Bharti et al., 2020; Wang et al., 2020b; Ou et al., 2021). In order to maximize function of PUE in wound healing, its sustained delivery by hydrogels is suggested. CS/PUE hydrogels have been utilized for purpose of wound healing in DM, and such hydrogels promote angiogenesis. MiR-29 upregulation leads to inflammation and delays wound healing in DM, while CS/PUE hydrogels reduce miR-29 expression to decrease levels of IL-1β and TNF-α to facilitate wound healing (Zeng et al., 2023). The newer types of hydrogels are thermosensitive CS hydrogels that can be used for insulin delivery. CS, gelatin, and HTCC have been exploited to develop thermosensitive hydrogels and have been loaded with clinical levels of insulin. These hydrogels displayed a low gelation time, uniform pore structure, and favorable swelling behavior that can encapsulate high levels of insulin and mediate its sustained release (Bahmanpour et al., 2021). The thermosensitive hydrogels derived from CS are capable of increasing expression levels of VEGF and reducing pro-inflammatory factors to accelerate wound healing in an animal model (Zhang et al., 2021). Loading FGF/VE-cadherin in CS/alginate hydrogels results in development of platforms that can enhance skin repair (Wei et al., 2022). Moreover, antibacterial peptides can be loaded in hydrogels to accelerate wound healing through promoting levels of VEGF, EGF, and CD31 and decreasing inflammatory factors (Huang et al., 2022). A

Table 3
The applications of CS-based hydrogels in DM therapy.

Hydrogel	Remark	Ref
Insulin-loaded chitosan nanoparticles/PLGA-PEG-PLGA hydrogel	Amelioration of neuropathy Decreasing scotopic B-wave amplitude Alleviation of retinal micro- and ultrastructural changes Decreasing apoptosis	Rong et al. (2019)
Thermosensitive chitosan hydrogel	Controlled release of insulin in 150 h Exerting hypoglycemic effect after subcutaneous injection	Ghasemi Tahrir et al. (2016)
Chitosan and carboxymethyl cellulose-based 3D multifunctional bioactive hydrogels	Loading curcumin in hydrogels for tissue regeneration impact Increasing number of fibroblasts, keratinocytes, and collagen Triggering epidermal junction	Shah et al. (2023)
Chitosan-based polyurethane hydrogel	Transplantation of mesenchymal stem cells derived from bone tissue for accelerating wound healing in DM	Viezzer et al. (2020)
Carboxymethyl chitosan-based hydrogels	Enhancing generation of Ki67 Increasing epithelization and collagen deposition Enhancing hair follicle generation Promoting neovascularization through increasing generation of CD31 and CD34	Hao et al. (2022b)
Polyvinyl alcohol-chitosan hydrogel	Loading honey bee venom in hydrogels Anti-inflammatory function Promoting wound healing process	Amin and Abdel-Raheem (2014)
Alginate/chitosan-based hydrogel	Delivery of polydeoxyribonucleotide as a gene product in wound healing acceleration High cellular uptake by skin fibroblasts	Jing et al. (2021)
Self-healing carboxymethyl chitosan/oxidized carboxymethyl cellulose hydrogel	Precise detection of glucose with sensitivity range of 100 μM to 5 mM Detection limit of 0.029 mM High biocompatibility of device	Shen et al. (2021)
Self-healing chitosan-based POSS-PEG hybrid hydrogel	A novel platform for wound dressing Antibacterial activity Enhancing proliferation and migration of cells	Li et al. (2023)
Genipin crosslinked chitosan-fiber hydrogel	Loading clemastine fumarate in hydrogels to induce its sustained release for promoting wound healing	Zuo et al. (2023)
Chitosan/silk hydrogel assembled with exosomes	Delivery of curcuma zedoaria polysaccharide to elevate collage deposition for promoting wound healing in diabetic rats	Xu et al. (2018b)
Carboxymethyl β-cyclodextrin grafted carboxymethyl chitosan hydrogel-based microparticles	Sustained release of insulin in time interval of 6–12 h to decrease glucose levels	Yang et al. (2020a)
Cellulose nanofibrils reinforced chitosan-gelatin based hydrogel	Loading nanoemulsion of oregano essential oil in hydrogels reduce scar generation and to promote granulation Enhanced epithelization	Razack et al. (2023)
Nitric oxide releasing chitosan-poly (vinyl alcohol) hydrogel	Stimulation of angiogenesis and hence, it is a promising platform for diabetic patients having chronic wounds	Zahid et al. (2019)
Composite hydrogel of chitosan/heparin/poly (γ-glutamic acid)	Loading superoxide dismutase in hydrogels that increase collagen deposition and promote wound closure Possessing antioxidant activity	Zhang et al. (2018)
Polyvinyl alcohol/chitosan composite hydrogels	Providing controlled release of Tibetan to enhance proliferation rate of HUVECs Enhancing collagen deposition and mediating anti-inflammatory activity	Wang et al. (2021b)
Photocrosslinkable chitosan hydrogel	Loading FGF-2 in hydrogels to enhance wound closure	Obara et al. (2003)
Thermosensitive Injectable Chitosan/Collagen/β-Glycerophosphate Composite Hydrogels	Encapsulation of mesenchymal stem cells in hydrogels to increase proliferation and paracrine secretion	Yang et al. (2020b)
A self-healing hydrogel based on crosslinked hyaluronic acid and chitosan	Acidic response and release of taurine molecules to transfer it into wound area Increasing proliferation Reducing number of inflammatory factors Future application for wound healing in DM	Zhou et al. (2022c)
Dextran/chitosan-based hydrogels	Functionalization of hydrogels with collagen and EGF Elevating proliferation of NIH 3T3 cells Increasing wound healing and closure	Hu et al. (2022a)

recent experiment has prepared CS/sodium alginate/velvet antler blood peptides that have high antioxidant activity and low hemolysis rate. They induce angiogenesis and proliferation of cells and decrease inflammation to promote wound healing. Mechanistically, such hydrogels stimulate PI3K/AKT/mTOR/HIF-1α/VEGFA and diminish TNF-α and IL-1β levels in promoting wound healing in DM (Hao et al., 2022a). In fact, when wounds are covered with hydrogels, they have ability to change the microenvironment in an optimal way to increase process of wound healing. Hydrogels can deliver rhEGF to wound site for promoting healing process. Furthermore, availability of drugs is enhanced by hydrogels, and they elevate proliferation and migration of cells. They inhibit DNA damage and reduce inflammation in wound healing acceleration (Chang et al., 2022). Therefore, hydrogels are promising carriers and structures for treatment of DM and its complications, particularly wound healing, as summarized in Table 2. In wound healing, CS-based hydrogels demonstrate high application because of their efficacy in enhancing collagen deposition (Li et al., 2021b), delivering therapeutic compounds such as NO (Razmjooee et al., 2022), enhancing skin tissue maturation (Patil et al., 2019), reducing ROS levels and exerting antibacterial activity (Pan et al., 2022), promoting epithelial layer formation (Ahmed et al., 2021), possessing immunomodulatory activity (Ragab et al., 2019), and promoting collagen maturation (Lee et al., 2021). All of these benefits advocate the application of CS-based hydrogels for wound healing acceleration in DM. However, more studies about using hydrogels for sustained release of therapeutic compounds in other complications of DM should be performed (Fig. 4 and Table 3).

6. Chitosan-based platforms in delivery of natural products

Phytochemicals and overall, plant-derived natural compounds are promising agents in DM therapy. However, one of their problems is low bioavailability, and in the treatment of some of the complications of DM, including neuropathy, they cannot pass through a biological barrier such as the blood-brain barrier. Therefore, nano-scale delivery systems are required for delivery of phytochemicals, which is the purpose of the current review. Thymoquinone (TQ) is a natural compound that has

been extensively utilized in DM therapy. TQ improves the function of liver and kidney in animal models, and neuroprotective factors such as BDNF, TH, and NGFR are normalized upon administration of TQ (Alkharfy et al., 2022). Furthermore, co-application of TQ and ischemic preconditioning can reduce apoptosis and pro-inflammatory factors including TNF-α and IL-1β to exert cardioprotective effects (Ran et al., 2021). CS-based nanostructures can improve function of TQ in treatment of diabetic rats. They had a particle size of 74.25 nm with an average size of 50 nm. Moreover, they provided a prolonged release of 78.5% of TQ. The TQ-loaded CS nanostructures did not demonstrate toxicity on normal lung cells, and they improved glycemia, dyslipidemia, inflammation, and oxidative stress in DM (Hosni et al., 2022). CS can be used for development of micro- and nano-scaffolds that are biocompatible and biodegradable, and after loading curcumin into scaffolds, they can increase wound healing and closure (Alavi et al., 2022). Moreover, CS and alginate can be co-used in development of nanostructures for DM therapy, and they enhance glucose uptake in HepG2 cells (Surendran and Palei, 2022). One of the ways is to develop CS nanostructures and then coat them with CS to mediate delivery of naringenin as a natural product. The encapsulation efficiency of alginate-coated CS nanostructures is more than 90%, and they mediate controlled release in response to pH. The nanostructures do not show toxicity on normal cells, and they can exert a hypoglycemic impact. Moreover, they are promising structures for oral delivery of naringenin (Maity et al., 2017).

P-coumaric acid is another compound used in the treatment of DM that reduces oxidative damage and ameliorates nephropathy in diabetic rats (Mani et al., 2022). Furthermore, the expression levels of MDA, TLR-4, IL-6, TGFβ1, and collagen will reduce in kidney upon p-coumaric acid administration to alleviate nephropathy (Zabad et al., 2019). A combination of p-coumaric acid and gallic acid is beneficial in decreasing oxidative damage in brain tissue, apoptosis inhibition, and alleviation of inflammation in treatment of diabetic neuropathy (Abdel-Moneim et al., 2017). The delivery of p-coumaric acid with CS nanoparticles in treatment of DM was performed. Such nanostructures had a particle size of 283 nm and important pharmacological activities, including antioxidant, anti-inflammation, antimicrobial, and anti-thrombotic properties that are beneficial in DM therapy (Venkatesan et al., 2022b). One of the most well-known natural compounds in DM therapy is curcumin, which reduces NF-κB expression while stimulating angiogenesis and osteogenesis, reducing diabetic osteoporosis (Fan et al., 2022). The nanoemulsions of curcumin have been developed to increase its potential in DM therapy, and such nanoformulations are able to reduce levels of inflammatory factors, COX-2, caspase-3, and NF-κB in brain injury alleviation (Saleh et al., 2022). Even analogs of curcumin, such as JM-2, can suppress NF-κB axis to reduce inflammation and ameliorate cardiomyopathy (Wang et al., 2022b). CS nanostructures are suggested to be promising factors for delivery of curcumin in DM therapy. Due to low particle size of curcumin-loaded CS nanostructures (74 nm), they can be internalized by cells. Moreover, curcumin-loaded CS nanoparticles have been able to enhance translocation of GLUT-4 and transfer it to the cell surface. Furthermore, this impact is due to Akt phosphorylation and subsequent expression of GSK-3β and its phosphorylation as a downstream target (Chauhan et al., 2018).

Berberine (BBR) is another natural compound for DM therapy, and one of its applications is the amelioration of diabetic nephropathy. BBR reduces the inflammatory indices, including IL-6 and TNF-α, and reduces oxidative damage by promoting SOD levels. Moreover, BBR has anti-fibrotic activity and decreases lipid levels, which are risk factors for diabetic nephropathy (Hu et al., 2022b). A combination of BBR and huangbai liniment has been used for diabetic wound healing that prevents apoptosis via caspase-3 down-regulation and enhances TIMP1 and TGFB1 levels (Zhang et al., 2022b). Moreover, BBR is beneficial in amelioration of diabetic atherosclerosis through promoting KLF16 and PPARα levels (Man et al., 2022). The lecithin-CS nanostructures have been beneficial in delivery of BBR, and they show synergistic effects in wound healing therapy. The designed nanostructures are able to decrease inflammation and enhance fibroblast proliferation. Furthermore, BBR-loaded CS-lecithin nanostructures enhance deposition of collagen and are promising factors for facilitating wound healing in DM (Panda et al., 2021). Therefore, delivery of phytochemicals by CS nanostructures improves their potential in DM therapy, as summarized in Table 4 and Fig. 5.

Table 4
The use of CS-based nanostructures for delivery of natural products in DM therapy.

Nanocarrier	Remark	Ref
Curcumin-loaded chitosan nanoparticles	Impregnation of CS nanostructures in collagen-alginate scaffolds Stimulation of contraction in wounds High epithelization Accelerating wound healing Inducing thick granulation tissue generation	Karri et al. (2016)
Cynometra cauliflora essential oil-loaded chitosan nanoparticles	High antimicrobial activity in diabetic wound microorganisms	Samling et al. (2022)
chitosan-encapsulated curcumin	Preventing injuries in kidney and heart in TIDM Reducing hypertrophy Decreasing nucleus enlargement	Sudirman et al. (2019)
Curcumin coated 3D biocomposite scaffolds based on chitosan and cellulose	Accelerating wound healing	Gupta et al. (2022)
Polydatin-loaded chitosan nanoparticles	Reducing oxidative damage and inflammation Down-regulation of IL-1β and TNF-α	Abd El-Hameed et al. (2021)
Chitosan-gallic acid conjugate	High thermal stability and crystallinity of conjugate Promoting α-glucosidase and α-amylase inhibitory activity	Liu et al. (2013)
Chitosan-sodium alginate-fatty acid nanocarrier	Increasing bioavailability of luteolin Protection of retinal cells against oxidative damage	Toragall and Baskaran (2021)
Polydatin-loaded chitosan nanoparticles	Decreasing oxidative damage and inflammation in diabetic nephropathy Down-regulation of COX-2 and NF-κB	Abd El-Hameed (2020)
Polydatin-loaded chitosan nanoparticle	Reducing lipid peroxidation product Enhanced glutathione content Promoting levels of SOD Anti-inflammatory function Alleviation of diabetic cardiomyopathy	Mostafa et al. (2021)

7. Chitosan-based nanoplatforms for delivery of genes

Gene therapy has emerged as a new kind of therapy for DM, and since genes can be degraded by enzymes and their blood circulation time is low, it is suggested to use nanostructures for their delivery. One of the benefits of CS-based nanostructures is their positive charge, which can mediate stable complexes with genes. Although the main emphasis is on drug delivery by CS nanostructures in DM therapy, there are a number of studies using CS nanostructures for gene delivery in DM therapy. GLP-1 is one of the genes that has similar actions to insulin, and one of its problems is its short half-life. The GLP-1 gene can be complexed with CS nanostructures, and after application in vivo in animal models, there was a significant enhancement in plasma insulin levels and also levels of GLP-1. These CS nanoparticles increased levels of GLP-1 in plasma by five times and normalized glucose levels (Jean et al., 2011). One of the

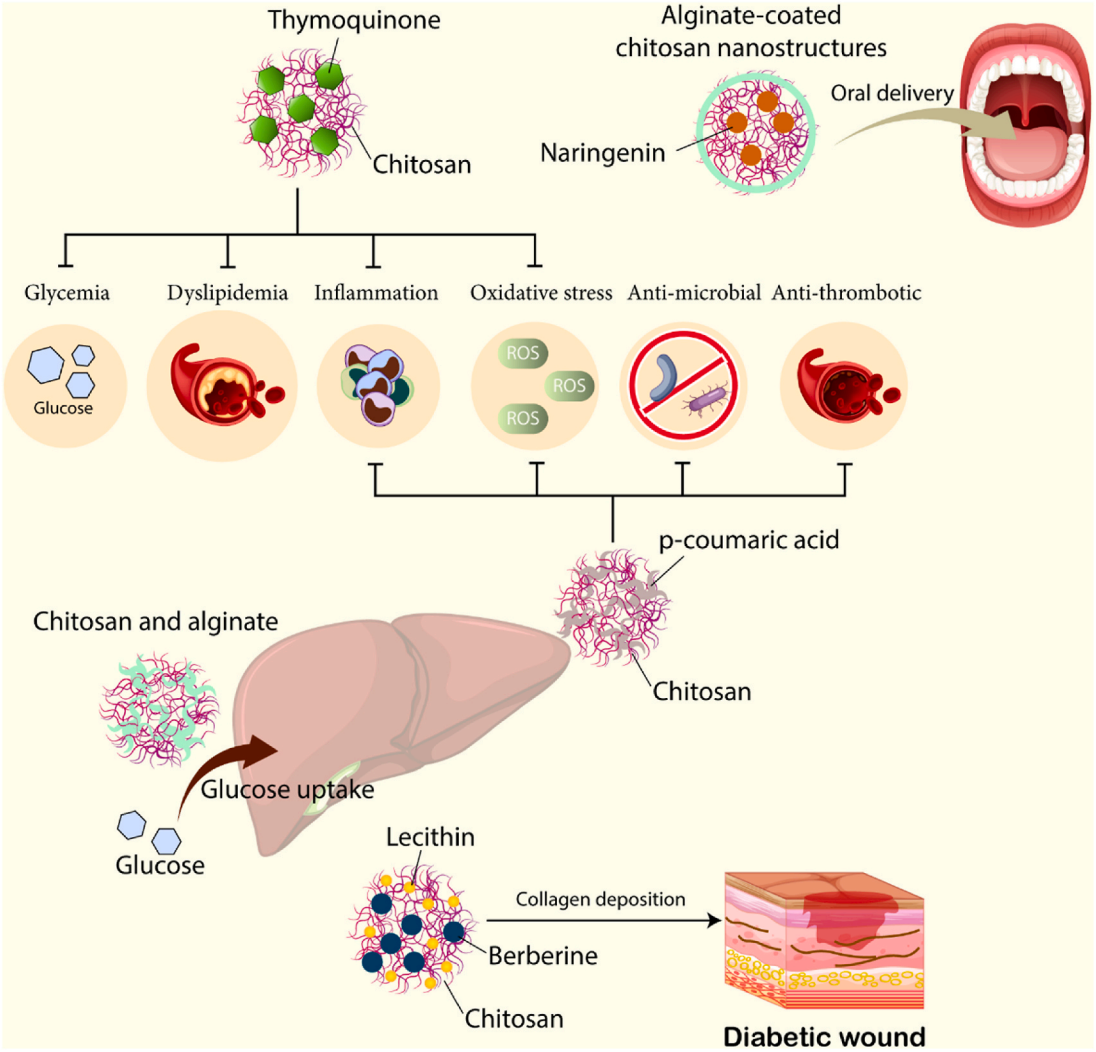

Fig. 5. The applications of CS nanoparticles in phytochemical delivery for DM therapy.

reasons that causes delayed wound healing in DM is poor levels of VEGF. The freeze-drying method was used to make CS scaffolds, which were then loaded with DNA coding for perlecan domain I and VEGF189. The DNA-loaded CS nanostructures accelerated wound healing in vivo, and they enhanced blood vessels. Moreover, DNA-loaded CS nanoparticles enhanced connective tissue matrix, and due to their angiogenesis induction activity, they are promising for wound healing acceleration in DM (Lord et al., 2017). The insulin gene is known as pCMV. Ins can be loaded on CS nanostructures, and after oral administration through gavage, the blood glucose levels were reduced. Moreover, the expression of insulin gene mRNA and insulin were only observed in treated groups (Niu et al., 2008).

8. Chitosan-based nanostructures and diabetic complications: A brief discussion

The previous sections provided a detailed discussion of using CS-based nanoplatforms for treatment of DM. To summarize, this section provides an overview of using such nanoparticles in treatment of diabetic complications. The most important application of CS-based nanoparticles is in wound healing. In diabetic patients, the process of wound healing is delayed, and there is an urgent need for therapies in management of chronic wounds. CS/PVA nanofibers have been developed for antimicrobial activity in wounds in DM, and they have a high odor absorbing ability. Such nanofibers have high biocompatibility, and 2 weeks of wound dressing revealed high potential of these dressings in DM (Ahmadi Majd et al., 2016). The immunomodulatory activity and long-term anti-inflammatory function have made CS-based platforms promising structures for wound healing (Maita et al., 2022). Another complication of DM is damage to liver and heart. The stabilization of selenium nanoparticles with CS results in upregulation of Bcl-2 and reduces Bax/Bcl-2 ratio in treatment of DM, reducing damage to liver and heart (Mohamed et al., 2021). The lipid and cholesterol metabolism can be regulated and monitored by CS, preventing injury to kidney in DM (Sutthasupha and Lungkaphin, 2020), and this is why focus has been directed towards development of CS-based nanostructures. Therefore, considering the potential functions of CS-based nanostructures, it is highly suggested to use them in DM therapy and alleviation of its complications, which are summarized in Table 5 and Fig. 6.

9. Conclusion and remark

The treatment of diabetes mellitus is not limited to the use of therapeutic medications; rather, interdisciplinary techniques for the delivery of therapeutic compounds should be offered. A lack of insulin secretion, for instance, can lead to the development of DM, which is why research has concentrated on the oral administration of insulin in the treatment of DM. However, the absorption of insulin is low, and it may be degraded in stomach. Therefore, there should be nanocarriers for insulin delivery in DM therapy. On the other hand, various kinds and

Table 5
An overview of using CS-based nanostructures in DM therapy and its complications.

Platform	Remark	Ref
Collagen/Chitosan Gels Cross-Linked with Genipin	A promising platform for wound dressing Enhancing collagen deposition Promoting hair follicle repair and sebaceous gland formation	Shagdarova et al. (2021)
Dual-functional hybrid quaternized chitosan/Mg/alginate	A wound dresser with antibacterial and angiogenic functions	Wang et al. (2021c)
Chitosan-Vaseline® dressing	The electrical induction enhances wound healing process	Wang et al. (2021d)
W/O Hypaphorine-Chitosan Nanoparticles	Decreasing inflammation to promote wound healing process	Qi et al. (2021)
Chitosan hydrogels loaded with silver nanoparticles and calendula extract	Particle size of 50–100 nm for silver nanoparticles Prolonged release of loadings for accelerating wound healing	Rodríguez-Acosta et al. (2022)
Chitosan/polyvinyl alcohol/zinc oxide nanofibrous mats	Preparation through electrospun method Antioxidant and antibacterial activities that are of importance for diabetic wound healing	Ahmed et al. (2018)
Chitosan/alginate/maltodextrin/pluronic-based mixed polymeric micelles	The curcumin-loaded nanostructures decreased glucose levels and improved wound healing	Akbar et al. (2018)
Stabilized-chitosan selenium nanoparticles	Reducing renal tissue damage Decreasing levels of Akr1B1, TGF-β, nestin, desmin and vimentin in reducing diabetic nephropathy	Khater et al. (2021)
All-Trans Retinoic Acid loaded Chitosan/Tripolyphosphate Lipid Hybrid Nanoparticles	Alleviation of diabetic nephropathy through elevating AMPK and LKB1 and decreasing creatinine, urea, TNF-α, ICAM-1, GM-CSF, VEGF levels	Asfour et al. (2021)

types of nanostructures have been introduced for purpose of DM therapy, and among them, biocompatible nanocarriers are of interesting since they can be used in the future in treatment of patients. The purpose of the current review was to evaluate the role of CS-based nanomaterials for DM therapy. The first application of CS-based nanoparticles is in delivery of insulin through oral route for treatment of DM patients. The application of CS nanocarriers allows the sustained release of insulin, improving its bioavailability and pharmacokinetics. The CS-based nanoparticles are able to protect insulin against degradation by stomach juice, which promotes its function in DM therapy. One of the newest advances in the field of DM therapy is the development of CS nanoparticles with mucoadhesive properties that can mediate better insulin release in DM therapy. However, CS-based nanoparticles cannot be used in treatment of all complications of DM, such as wound healing. In this case, hydrogels have been developed for sustained and prolonged release of therapeutic agents. Due to the biocompatibility of CS, hydrogels have been developed based on CS, and such biodegradable hydrogels with low toxicity features can be employed for DM therapy, especially for the treatment of wound healing, which is a major complication. Plant-derived natural products have attracted much attention for treatment of DM mellitus, but their bioavailability is poor and their therapeutic index is limited. Therefore, it is highly suggested to use nanoparticles for delivery of phytochemicals, and in this review, it was found that the delivery of phytochemicals by CS-based nanoparticles improves the potential of DM therapy. Since CS-based nanoparticles demonstrate high efficiency in DM therapy, future studies can focus on using them for treatment of DM patients in clinical trials. One of the most prominent advances is the development of CS-based hydrogels for DM therapy. The reason for using CS in development of hydrogels is to have platforms with high biocompatibility so that their future clinical application for diabetic patients is paved. Moreover, other biopolymers, such as hyaluronic acid, can be used for the synthesis of hydrogels, and since hyaluronic acid has antibacterial activity, this can improve potential for wound healing. More importantly, one of the benefits of hydrogels is their ability to sustain the release of therapeutics that can be genes or drugs, and when wounds are dressed with hydrogels, they mediate prolonged release of drugs to increase wound healing acceleration. The most common use of hydrogels is wound healing in diabetic patients, but since hydrogels possess sustained release of therapeutics, it is suggested to use them also for treatment of other diabetic complications.

The CS-based nanostructures have been used extensively in therapy of various human diseases. The first benefit of nanostructures fabricated from CS and casein is that they are biodegradable (Lin et al., 2022). The CS-based nanostructures are promising carriers for delivery of chemotherapy drugs in cancer therapy and they reduce IC_{50} along with impairing tumorigenesis in vivo (Vikas et al., 2022). The CS-based nanoparticles can promote accumulation of drug at cancer site and demonstrate high cytotoxicity (Wang et al., 2022c). Furthermore, CS can be used for synthesis of hydrogels in loading other nanostructures. For instance, gelatin and CS have been used to prepare thermosensitive hydrogels in loading 5-FU-alginate nanostructures for purpose of skin delivery (Nawaz et al., 2022). Moreover, when LL37 is delivered by CS nanostructures, the ability as antibacterial and antifilm compound increases (Rashki et al., 2022). The bacteria are capable of developing multidrug resistance and mannose-functionalized CS/PLMA nanomaterials are able to overcome this condition (Arif et al., 2022). Curcumin-loaded CS nanostructures have been also promising for antioxidant edible coating (Shen et al., 2022). CS-based nanoparticles have shown capability in treatment of ocular diseases (Kalam et al., 2022) and they can also deliver genes in disease therapy (Moghadam et al., 2022). Since CS-based nanostructures have been extensively used in treatment of various diseases, the current paper was dedicated in understanding role of these nanoparticles in treatment of DM. The oral administration of antidiabetic drugs such as Exenatide can be facilitated using CS-based nanomaterials (Yang et al., 2022). The implant osseointegration in TIIDM can be accelerated using CS-PLGA microspheres embedded with exendin-4 (Shi et al., 2022). Because of antioxidant and anti-apoptotic function of CS-based nanoparticles, they can protect heart cells in DM (Wardani et al., 2022). Furthermore, polyelectrolyte complexes can be designed from CS and fucoidan to provide controlled release of growth factors in increasing growth and collagen accumulation in DM (Rao et al., 2022). Although CS-based nanostructures are used extensively in DM therapy (Saraswati et al., 2022; George and Shrivastav, 2023), the main application of these nanomaterials is in accelerating wound healing in DM through their photothermal, antimicrobial, anti-inflammatory, antioxidant, angiogenic and anti-apoptotic functions and properties (Yu et al., 2022; Hou et al., 2022; Lv et al., 2022; Sanapalli et al., 2023; Hajati Ziabari et al., 2022; Perteghella et al., 2023). Moreover, since insulin is widely used for DM therapy, smart CS/alginate nanostructures have been developed for insulin delivery to improve its efficacy (Zhang et al., 2022c). Hence, CS is a versatile compound in treatment of DM and based on the discussions of this paper, it can be concluded that CS-based nanoarchitectures are promising candidates.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence

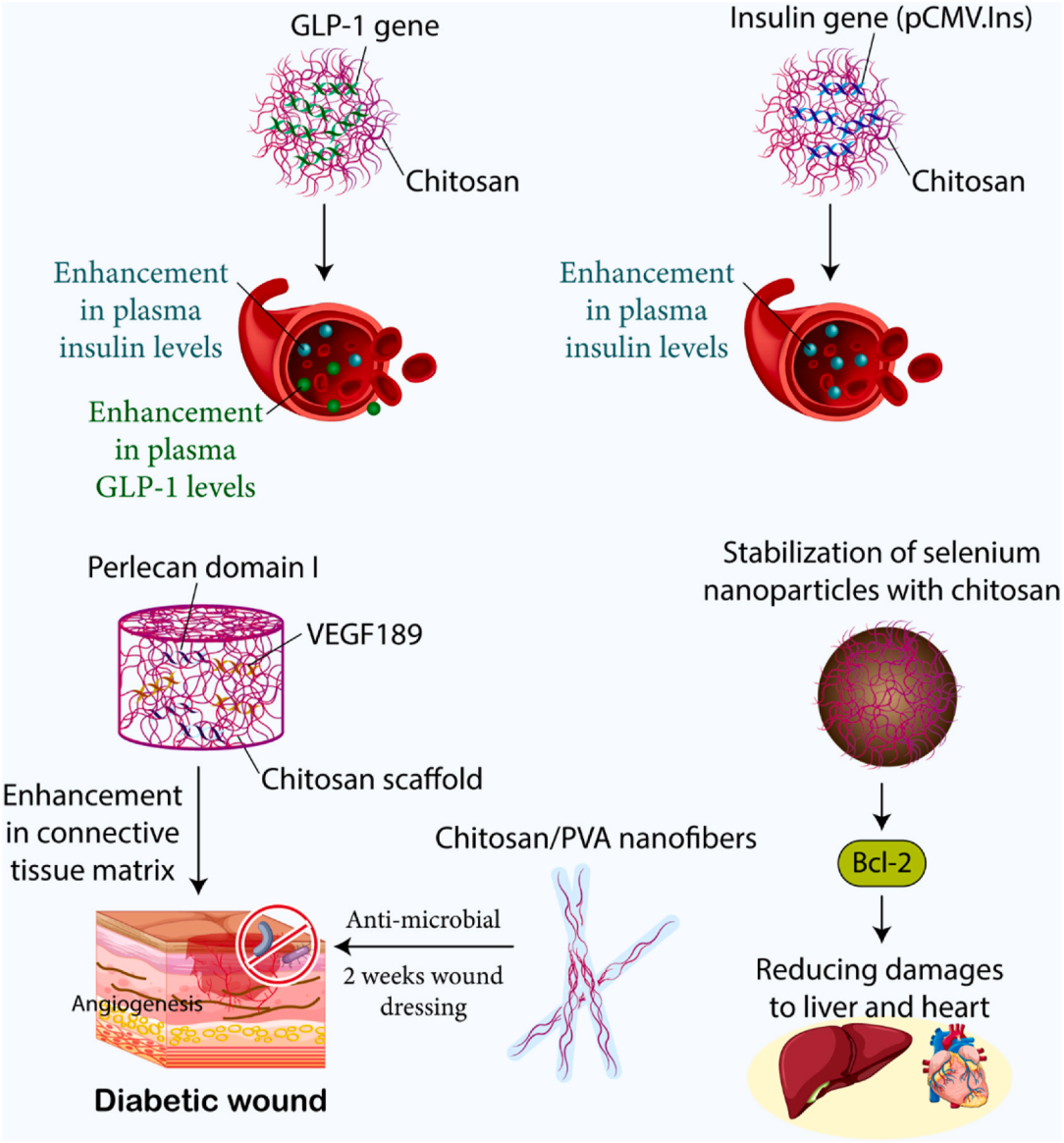

Fig. 6. CS-based nanostructures for gene delivery and alleviation of diabetic complications.

the work reported in this paper.

Data availability

No data was used for the research described in the article.

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