


Current Strategies and Potential Prospects for Nanoparticle-Mediated Treatment of Diabetic Nephropathy

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Abstract: Diabetic nephropathy (DN), a severe microvascular complication of diabetes mellitus (DM), is the most common form of chronic kidney disease (CKD) and a leading cause of renal failure in end-stage renal disease. No currently available treatment can achieve complete cure. Traditional treatments have many limitations, such as painful subcutaneous insulin injections, nephrotoxicity and hepatotoxicity with oral medication, and poor patient compliance with continual medication intake. Given the known drawbacks, recent research has suggested that nanoparticle-based drug delivery platforms as therapeutics may provide a promising strategy for treating debilitating diseases such as DN in the future. This administration method provides multiple advantages, such as delivering the loaded drug to the precise target of action and enabling early prevention of CKD progression. This article discusses the development of the main currently used nanopatforms, such as liposomes, polymeric NPs, and inorganic NPs, as well as the prospects and drawbacks of nanopatform application in the treatment of CKD.

Keywords: diabetic nephropathy, DN, nanopatform, route of administration

Introductions

DN is a chronic complication of diabetes and the leading cause of end-stage kidney disease, a specific microvascular disease that is the main cause of death in type 1 DM (T1DM).^{1,2} In type 2 DM (T2DM), DN greatly increases mortality and disability in patients with diabetes, and its degree of malignancy is second only to that of cardiovascular disease.³ Recent data has indicated that approximately 9% of the world's adult population is affected by DN, and the prevalence of DN is nearly 70% in patients with diabetes; 592 million people have been predicted to have diabetes worldwide by the year 2035.⁴⁻⁶ As many as 47.66% of patients with diabetes have been estimated to have DN, thus posing a major challenge in treating DM. DN is also the primary cause of kidney failure in patients with diabetes.⁷

DN is more common in patients who have had T2DM for more than a decade, whose vascular damage is caused by hyperglycemia and affected by several pathways, such as oxidative stress, inflammatory response, endoplasmic reticulum (ER) stress.⁸ Hyperglycemia may be a direct trigger of inflammation, endoplasmic reticulum stress, and mitochondrial dysfunction, thus leading to excessive reactive oxygen species (ROS) production. Diabetic complications occur as a result of the accumulation of cellular damage caused by oxidative stress, and inflammatory infiltrates further lead to the release of ROS and proinflammatory cytokines.^{9,10} Glycemic control often relies on several strategies, such as lifestyle changes, low-sugar diets, chemical hypoglycemic agents, and herbal preparations; multiple medications are often required to achieve adequate glycemic control in most patients.¹¹ Diabetes-induced fibrogenesis is driven by inflammation. Statins, vitamin D, and sodium-glucose cotransporter 2 (SGLT2) inhibitors, such as glibenclamide, are now routinely considered anti-inflammatory medications.¹² MCP-1, also known as chemokine ligand 2 (CCL2),

produced by podocytes, plays a central role in DN inflammation. Elevated TRB3 expression significantly inhibits MCP-1 production and may be a therapeutic target for DN anti-inflammation.¹³ A relationship between oxygenation stress and ER stress is often thought to exist, because increased ROS production destabilizes the luminal environment of the ER, thereby causing ER stress.¹⁴ In addition, antioxidants have been found to decrease ER stress through the elimination of ROS and oxidative stress.¹⁵

The occurrence and development of DN are also thought to be related to genetic susceptibility, insulin resistance, low-grade inflammatory state, vascular endothelial cell dysfunction, and coagulation abnormalities.¹⁶ A major pathological abnormality in DN is mesangial expansion, the accumulation of extracellular matrix (ECM) within the mesangium, followed by tubulointerstitial fibrosis and glomerulosclerosis.¹⁷ The above pathological features may be adverse reactions of long-term extensive use of hypoglycemic drugs. At present, conventional treatments include strict weight control, blood sugar control, lipid and blood pressure reduction, protein intake restriction, smoking cessation, treatment goals of A1c < 7% and <130/80 mmHg, and elimination of albuminuria.¹⁸ However, commonly used drugs such as renin-angiotensin system blockers, metformin, long- and short-acting insulin often have high blood clearance, low effective circulating drug concentrations, and non-targeted drug delivery, thus leading to the development of end-stage renal disease in patients with DN.¹⁹ The end-stage renal disease stage of DN requires dialysis treatment, which accounts for 35% of new cases of dialysis treatment worldwide, and 13–25% of patients experience a fall after starting chronic hemodialysis, thus severely affecting quality of life in patients with DN.²⁰

With developments in nanotechnology and biochemistry, a nanoplatform drug delivery system can be built in which anti-diabetic medicine can be broken down, implanted, encapsulated, or attached to nanoparticles.^{21,22} In addition, nanoparticles modified by active targeting molecules can also contribute to efficient drug delivery. Transported drugs pass through the immune clearance system, thus eliminating unwanted off-target effects and improving treatment effects.^{22,23} Therefore, the development of nanoparticle-mediated treatments is urgently required to overcome the adverse effects of conventional drug delivery methods. The current status of research and development in DN treatment is introduced and described in [Table 1](#). This review presents the most recent developments in various nanoparticle technologies and their applications in DN treatment, as well as a new vision for the future development of nanoplatforms.

Research Progress in Nanoplatforms in the Treatment of DN

Liposomes

The first synthesis of lipid NPs (LNs) occurred in the early 1990s, in a new era of searching for a new generation of nanocarriers. Given their multiple advantages of biodegradability, biocompatibility and low immunogenicity, LNs are regarded as a highly promising route of drug delivery. A liposome consists of either one (unilamellar liposomes) or several (multilamellar liposomes) lipid bilayers.²⁴ Liposomes encapsulate hydrophilic drugs within the aqueous core of the bilayer membrane, and hydrophobic drugs are incorporated within the acyl chains.²⁵ Relevant studies have indicated that liposomes allow for efficient incorporation of lipophilic drugs, thus not only enhancing membrane permeability, and consequently improving controlled release of active ingredients and increasing drug bioavailability, but also enabling the controlled delivery of a drug to specific tissues through surface functionalization with targeting molecules.^{26,27}

Optimal nanoparticle sizes are also important, because the kidneys rapidly clear NPs less than 10 nm in size. However, NPs larger than 150 nm are recognized by the immune system and cleared.²⁸ In addition, NPs of certain sizes can be selected by the kidneys. Owing to the presence of the glomerular filtration membrane in the kidney, particles of specific sizes can be isolated in the renal thylakoid membrane. Particles of 30–80 nm are effectively retained in the kidney, thus avoiding excretion from the urinary system and low bioavailability due to capture by the liver and spleen.⁴ Given that hyperglycemia promotes high levels of ROS, thus resulting in glucose-mediated damage, the mechanisms of damage include an increase in polyol pathway flux, and AGE formation and hexosamine pathway flux with activation of receptor of advanced glycation end-products (RAGE) and protein kinase C isoforms.²⁹ Among the many antioxidants that may delay overproduction of ROS, phenolic compounds play important roles in ROS detoxification while maintaining the oxidation reduction (redox) balance to facilitate cellular homeostasis. Notably, in some cell lines and tissues, myricitrin appears to be able to decrease oxidative stress and

Table 1 Examples of Preclinical Studies About Different Nanoplatform in the Treatment of DN

Nano Carrier	Cargo	Target	Mechanism	Strengths	Reference
1. Liposomes					
Solid lipid nanoparticle (SLN)	Myricitrin	Kidney cell	Myricitrin targeted into kidney cell with SLN to inhibit the expression of TGF- β and reduce oxidative stress and cytotoxicity.	Compared with traditional oral polyphenols, lipid nanoparticles facilitate their passage through cell membranes and improve bioavailability.	Akram et al ³¹ Chen et al ³⁰
Kidney-targeted rhein (RH)-loaded lipid nanoparticles	Rhein (RH)	Renal tubular cells, endothelial cells, mesangial cells, and podocyte	KLPPR promoting quick cellular internalization of the renal tubular cells, endothelial cells, mesangial cells, and podocytes uptake and endocytosis through a non-lysosomal pathway and rhein's antioxidant and anti-inflammatory properties can protect the kidney from DN.	KLPPR alleviates hepatotoxic side-effects of RH and improves bioavailability through excellent kidney-targeted distribution.	Wang et al ⁴ Ghorbani et al ³⁵
Apigenin-loaded Solid Lipid Nanoparticle	Apigenin	Kidney cell	Apigenin-SLNP can enhance nuclear factor erythroid 2-related factor 2/heme oxygenase-1 pathway to reduce the ROS and inflammation.	SLNP improve biodistribution sensitivity and specificity of Apigenin and greatly increases its bioavailability, while reducing its pharmacological toxicity.	Li et al ³⁸ Wu et al ³⁷
2. Polymeric					
2.1 Chitosan					
Trimethyl chitosan nanoparticles	Oral insulin	Insulin dependent tissues including kidney	Cs results in mucosal adhesion and increasing absorption through the ionic interaction between cationic amine groups of it with the anionic groups at the epithelial cell surface. pH-sensitive of Alginate swells in the alkaline pH of the intestine while is stable at low pH of other organs.	Trimethyl chitosan nanoparticles with higher solubility does not have side effects as injected insulin such as needle phobia, pain, skin bulges, allergic reactions, common infections and so on.	Azar et al ⁹ Li et al ⁴⁵
ChAuNps /PLGA	Oral insulin	Insulin dependent tissues including kidney	Mucus-penetrating nanoparticles particularly paired with biocompatible and mucoadhesive polymers like chitosan and PLGA will cause the nanoparticles to adhere to the intestinal membrane, which makes it easier for nanoparticles to engage with mucoid membranes, prompting tight junctions to change completely and then transfer the linked insulin along the paracellular route.	The nanocarrier achieves longer-term insulin release and the oral delivery of insulin via nanoparticles effectively avoid painful and traumatic subcutaneous delivery in the treatment of postprandial hyperglycemia.	Asal et al ⁴⁶ Khan et al ⁴⁸
Chitosan-Nanoparticles	Polydatin (resveratrol-3-O- β -mono-D-glucoside)	Kidney cell	POL-NPs ameliorates the inflammatory responses by downregulation of NF- κ B and consequently COX-2 to attenuate the DN which also restore the normal equilibrium between pro- and anti-inflammatory cytokines through modulating of the pro-inflammatory response in the kidney. It also significantly attenuated renal injury through the stronger antioxidant properties of polydatin.	POL-NPs new formula is biocompatible and can successively ameliorate nephropathy in diabetic rats than free POL.	Abeer et al ⁴⁹ Latos-Brozio et al ⁵¹

(Continued)

Table 1 (Continued).

Nano Carrier	Cargo	Target	Mechanism	Strengths	Reference
Brij-grafted-chitosan (BC with grafted degree of 12%)	Berberine (BBR)	Intestinal epithelium and kidney	BBR-BC12-NPs enhanced intestinal permeability of BBR by facilitating paracellular transport and inhibited PGP-mediated drug efflux.	The BC-NPs enhances the relative oral bioavailability of BBR in rats and the therapeutic potency of BBR in renal function and histopathology.	Xiong et al ⁶ Yu et al ⁵⁵
2.2 Polylactic acid blockcopolymer pla-P85-PLA	Oral insulin	Gastrointestinal cells	P85 block on the surface of PLA-P85-PLA vesicles could exhibit high permeation characteristic to the cell membrane of the intestine due to their amphiphilic property and the active transcellular transport of nanoparticles begins with an endocytic process that occurs at the apical cell membrane and then the particles transport through the cells and release at their basolateral pole.	PLA-P85-PLA vesicles can maintain the glucose level over a longer time than for the normal subcutaneous injection of free insulin. Meanwhile, its degradation products can enter the tricarboxylic acid cycle or be removed from the body by the kidneys.	Xiong et al ⁶¹ Mohamed et al ⁶²
PLA Nanoparticles	Tinospora cordifolia (Willd.)	Glomerulus and its blood vessels	TC-PLA NPs may impart the therapeutic potential through enhanced antioxidant function of TC and reduced the inflammatory rates either alone or via bioactive compound synergism.	TC-NPS is an alternative medicine to avoid adverse side effects and expensive therapy while enhancing the protection of the body due to their hepatoprotective capacity.	Ragavee et al ⁶⁵ Alajmi et al ⁶⁴
3. Inorganic NPs 3.1 Nano-oxides USPIO-PEG NP	Anti-LOX-I	Renal LOX-I	Activated macrophages expressing LOX-I selectively accumulate LOX-I-targeted PEG-coated USPIO nanoparticles simultaneously. Signal reduction induced by LOX I-targeted USPIOs administration accurately reflects the inflammatory response characteristic of early DN.	It shows good cellular internalization and can detect noninvasively inflammatory renal lesions in early DN.	B. Luo et al ⁷¹ Li et al ⁷³
C-Mn ₃ O ₄ NP	C-Mn ₃ O ₄	Mitochondria in kidneys	C-Mn ₃ O ₄ NPs can scavenge intracellular ROS, inhibit apoptotic trigger, prevent loss of antioxidant enzymes to maintain high cell viability by acting as a protector of mitochondria, the master regulator of cellular redox equilibrium.	C-Mn ₃ O ₄ NPs long-term attenuate renal injury and tubuleintestinal fibrosis showing not any toxicological implications.	A. Adhikari et al ⁷⁷ Adhikari et al ⁷⁹
ZnO NPs	ZnO	Kidney	ZnONP decreases the expression of TGF-β1, collagen IV, and fibronectin and increases the expression of MMP-9 in the diabetic kidney with low toxicity.	ZnONPs can improve renal function, by inhibiting renal fibrosis, oxidative stress, inflammation, and abnormal angiogenesis and the ameliorating podocyte injury to ameliorate the renal damage.	Alomari et al ⁸⁵ Cao et al ⁸¹
3.2 Nano-Composite Oxides MET-HMSN-CeO ₂ NPs	Cerium oxide and metformin	Kidney	Ceria with surface provide high oxygen storage abilities and can scavenge free radicals via the self-circulation of redox reaction and MET as glucose production inhibitor can inhibit glucose production.	Combined antioxidative with antidiabetic activities, nanoparticle administration can exhibit specially nephroprotective ability without causing major side effects.	Tong et al ⁹¹ Schöneborn et al ⁹³

(Continued)

Table I (Continued).

Nano Carrier	Cargo	Target	Mechanism	Strengths	Reference
3.3 Nanometals and Nanoalloys					
AuNPs	Au	Kidney	AuNPs prevents TNF- α over expression while reduces the renal oxidative stress by increasing the activities of renal SOD and catalase and by reducing the tissue MDA level and can stay in the blood circulation for a longer period of time.	AuNPs prevents the adverse effects of hyperglycemia in renal tissue by preventing the accumulation of ECM proteins and the amelioration of podocyte injury without showing no cytotoxicity in human cells.	Alomari et al ⁹⁹ Xia et al ¹⁰¹
PPE-AuNP	Au	Kidney	PPE-AuNP suppress the hyperactivation of RAGE-guided NOX-4/p47phox activation and reducing the production of ROS hollowed by the dephosphorylation of MAPK/ NF- κ B/ STAT3-mediated proinflammatory burden.	PPE-AuNP is economic alternative to alleviate DN by exhibiting endogenous antioxidant response.	K. Manna et al ⁹⁵ Liu et al ¹⁰¹
AuNP	AuNP	Exosomal urinary miRNAs	Due to adsorption of miRNA probe hybrid on the AuNPs, thus preventing salt-induced aggregation of AuNPs test solution is red While in the presence of non-specific miRNA, only short probe molecules is adsorbed to the AuNPs, test solution is blue.	Its sensitivity is comparable to that of qRT-PCR but cost-effective.	Nossier et al ⁵ Tan et al ¹⁰⁶
Momordica charantia silver nanoparticles	Silver nanoparticles	Kidney	Both negative regulation the PI3K/Akt pathway by down-regulating PTEN gene expression, and inhibition the activation of JAK/STAT signaling by up-regulating SOCS3 expression to alleviate the inflammatory response in DN.	Silver nanoparticles protect kidney through the modulation of different inflammatory signaling pathways and has good antibacterial properties.	Elekofehintdeg et al ¹¹⁰ Kheybari et al ¹⁰⁸
AgNPs@PVP and AgNPs@PVA	Silver nanoparticles	Creatinine	The color changes in solutions containing AgNPs@PVP and AgNPs@PVA caused by different concentrations of creatinine, this color change is measured using a designed optical imaging and image-processing system (colorimetric), and the amount of creatinine (quantitatively and qualitatively) is displayed in real time.	Such method is simple to use and much lower cost than that of other creatinine measurement methods.	Elekofehinti et al ¹¹²
3.4 Other Inorganic NPs					
Quantum Dots		Glomerular mesangial cells	Mesangial cells with high endocytosis activity uptake Quantum Dots.	PEG-coated Qdots preferential enriched in the renal mesangium upon intravenous application set New Paths for future therapeutic applications of drug-loaded nanomaterials for the treatment of kidney-associated diseases like DN.	Pollinger et al ¹¹⁴

(Continued)

Table I (Continued).

Nano Carrier	Cargo	Target	Mechanism	Strengths	Reference
Quantum dots	AR antibody and TLR4 antibody		QDs probes Correspondingly combined with AR antibody and TLR4 antibody, and ultraviolet light could simultaneously excited Two colors of QDs, then is imaging in IHC.	Compared with conventional IHC, QD-IHC can save lot of time and explore the various pathogenesis of DN.	Liu et al ¹⁷ Xu et al ¹³
4. Biological nanoparticles Influenza A virus Nps	Cinaciguat (CCG)	Mesangial sites in the kidney.	NPs active drove CCG to mesangial sites, CCG-carrying NPs is degraded by the endolysosome and cinaciguat (CCG) can specifically bind and activate soluble form of the guanylate cyclase (sGC), then transforms guanosine triphosphate (GTP) to 30.50-cyclic guanosine monophosphate (cGMP) which down regulation of excessive glomerular fibrosis and hyperproliferation	For same dosing effect, the dose carried by NP is only 10% compared with the free CCG concentration.	Daniel Fleischmann et al ¹²³ Fleischmann et al ¹²⁴

Abbreviations: SLN, Solid lipid nanoparticle; RH, rhein; PCL-PEI, polycaprolactone-polyethyleneimine; KLPPR, kidney-targeted RH-loaded lipid nanoparticles with a yolk-shell structure composed by PCL-PEI-based cores and KTP-modified lipid layers; ROS, reactive oxygen species; CS, chitosan; PLGA, poly lactic-co-glycolic acid; ChAuNP/PLGA, CS gold NPs functionalized with PLGA; POL-NPs, Polydatin-loaded Chitosan-Nanoparticles; BBR, Berberine; BC, Brij-grafted-CS; PLA, poly (D, L-lactide); PLA-P85-PLA, PLA segments to both ends of a Pluronic P85 copolymer to generate an amphiphilic vesicles; TC, *Tinospora cordifolia*; TC-PLA NPs, TC-PLA nanoparticles; PEG, polyethylene glycol; USPIO-PEG NPs, ultrasmall superparamagnetic iron oxide PEG-coated NPs; C-Mn₃O₄ NPs, citrate functionalized Mn₃O₄ nanoparticles; HMSN, hollow mesoporous silica nanocomposite; MET, metformin; PPE-AuNP, peel extract-stabilized gold nanoparticle; PVP, Polyvinyl pyrrolidone; PVA, Polyvinyl alcohol; AgNPs@PVP, PVP-coated silver nanoparticles; AgNPs@PVA, PVA-coated silver nanoparticles; PPE-AuNP, peel extract-stabilized gold nanoparticle; QDs, quantum dots; AR, Aldose reductase; TLR4, Toll-like receptor 4; sGC, soluble form of guanylate cyclase; GTP, guanosine triphosphate; cGMP, cyclic guanosine monophosphate; CCG, cinaciguat; IHC, immunohistochemistry.

cytotoxicity.³⁰ To overcome the problem of low bioavailability of polyphenols with high polarity, research has been conducted on combining polyphenols. Ahangarpour et al³¹ have designed and used the cold homogenization method to prepare SLNs of myricitrin. In a mouse model of DN induced by streptozotocin-nicotinamide (STZ-NA), compared with a diabetes group, moderate and low doses of myricitrin have been found to be more effective in decreasing expression of the TGF- β gene. TGF- β is a key intermediary that exerts its effects by binding its receptors on the cell membrane, TGF- β R I and RII, thus promoting the phosphorylation of downstream factors, such as SMAD proteins, and stimulating glomerular cells to synthesize ECM, and TGF- β is associated with abnormal renal cell proliferation, glomerular hypertrophy, ECM protein accumulation, renal interstitial fibrosis, and damage to the glomerular filtration barrier.³² In SLN-treated diabetic mice, by decreasing oxidative stress through increasing antioxidant enzyme levels, LNs clearly ameliorate various pathological conditions in DN.³¹ This superior therapeutic effect by improving drug bioavailability is often found in the use of LNs in targeted organ therapy.³³ Compared with conventional NPs, which have low bioavailability because of their low retention in the kidneys, LNs can be flexibly sized to enhance retention on the basis of differences in target organ filtration, and can be chemically modified to enhance their affinity toward target sites, to minimize drug loss from the bloodstream.³⁴ Evidence indicates that rhubarb acid has antidiabetic effects, as well as anticancer, renoprotective, cardioprotective, and hepatoprotective activities. This plant may have the potential to protect body tissues, particularly the liver and kidneys, from environmental toxins and drug side effects.³⁵ Wang et al⁴ have used a yolk-shell structure with polycaprolactone-polyethyleneimine (PCL-PEI) as the core and lipid layer modified with kidney-targeting peptide (KTP) and successfully fabricated kidney-targeted rhein (RH)-loaded LNs (KLPPR). KTP (sequence: CSAVPLC) was modified to promote rapid cellular internalization by renal tubular cells, endothelial cells, mesangial cells, and podocytes through uptake and endocytosis via a non-lysosomal pathway (Figure 1). The size of 75.4 ± 2.9 nm has been demonstrated to determine the kidney tissue distribution and specificity of NPs in DN model mice.^{4,36} In the case of

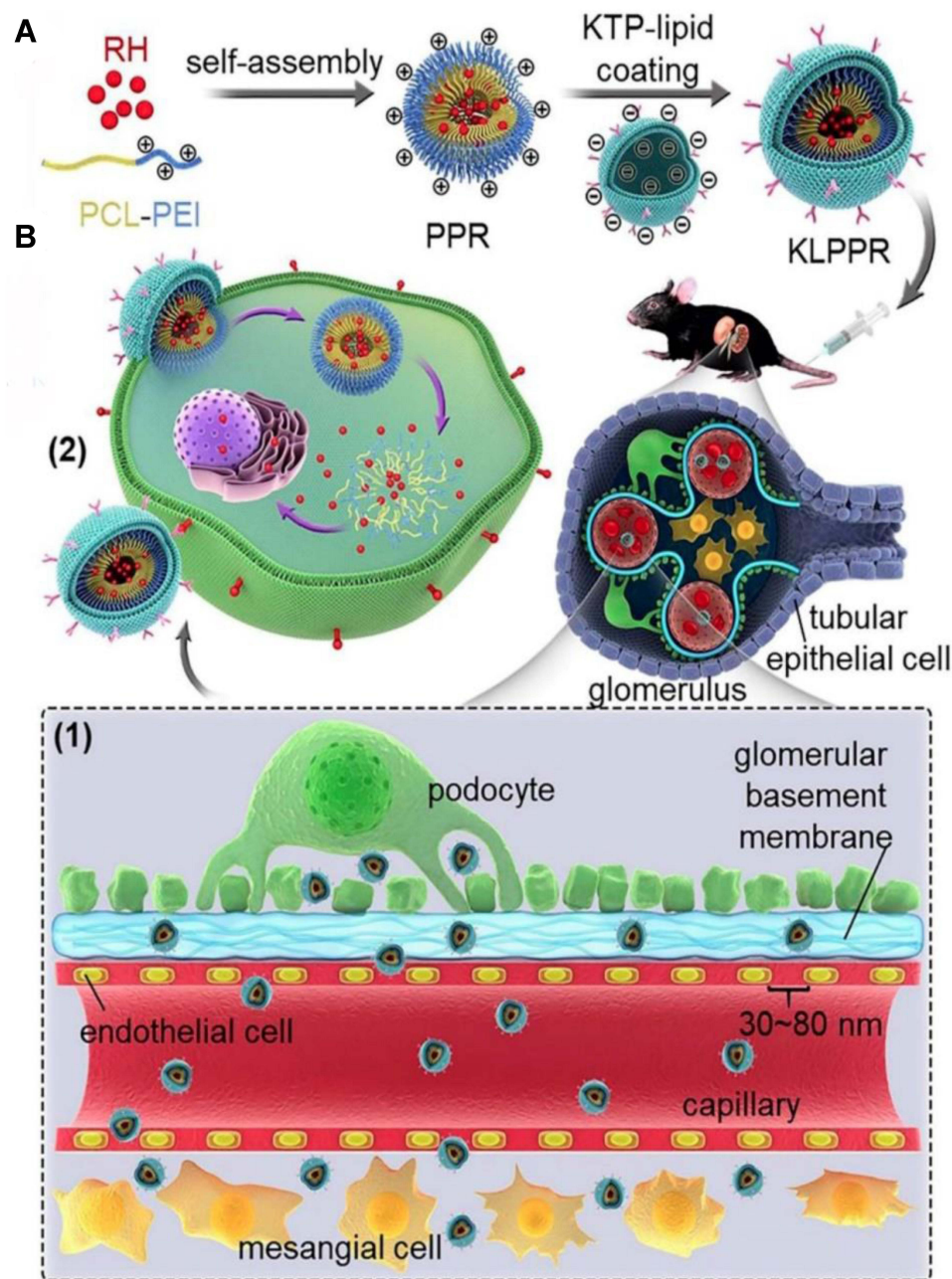


Figure 1 Generalized map of kidney-targeted drug transport based on KLPPR lipid nanoparticles.

Notes: (A). KLPPR composed of a negatively charged KTP-modified lipid layer and a positively charged rhin-loaded polycaprolactone-polyethyleneimine nanocore by electrostatic interaction. (B) Application of the two-step nanoscale cascade concept: (1) control the size of KLPPR in the range of 30–80 nm to ensure transport across the glomerular filtration membrane to the kidney; (2) KTP-modified membrane fusion promotes uptake and internalization by renal cells and increases the renal retention of KLPPR. Reproduced from Wang G, Li Q, Chen D et al, Kidney-targeted rhin-loaded liponanoparticles for diabetic nephropathy therapy via size control and enhancement of renal cellular uptake. *Theranostics*. 2019;9(21):6191–6208⁴.

Abbreviations: KTP, kidney-targeting peptide; KLPPR, kidney-targeted RH-loaded liponano particles with a yolk-shell structure composed by PCL-PEI-based cores and KTP-modified lipid layers.

TGF- β 1, KLPPR shows more favorable pharmacological efficacy of RH than LPPR in a mouse model of DN; moreover, KLPPR significantly regulates the abnormal expression of proteins, thereby improving renal function in the kidney. The drug delivery system not only alleviates the hepatotoxic adverse effects of RH in clinical settings but also increases bioavailability through excellent kidney-targeted distribution. Notably, apigenin NPs are approximately 4.96 times more bioavailable than raw apigenin, but they have no toxic effects on rats' organs.³⁷ To decrease

the high oral intake of apigenin and overcome the limitations of its poor stability in the blood, low absorption and high loss from the urinary system, Li et al³⁸ have artificially increased the bioavailability of apigenin by mixing it into solid LNs through a microemulsification method. They have demonstrated that apigenin-SLNP activates the expression of nuclear factor- κ B related factor 2 and haematoxylin-1, thus resulting in an anti-apoptotic effect. Simultaneously, the anti-inflammatory effect increases the expression of Nrf2 and HO-1. The combination of apigenin and LNs is less toxic than other engineered formulations, thus indicating great potential for clinical applications. More promisingly, such combinations with weak toxic effects have shown similar pharmacological activity to that of metformin (MET), thus encouraging the application of NPs in renal injury studies. According to the results outlined above, the biodistribution sensitivity and specificity in lipid-modifying therapy can be significantly improved while decreasing nephrotoxic adverse effects. In vitro and in vivo studies have been performed primarily in mice and rats in preclinical trials. Nonetheless, before human testing, the drug will require a comprehensive evaluation of safety pharmacology and drug toxicology.

Liposomes were the first nanomedicine technology to reach the clinical application stage in the past decade.³⁹ Liposomes' biocompatibility and biodegradability make them suitable for clinical applications.⁴⁰ However, long-term stability and membrane permeability are major challenges with liposome systems. Some studies have shown that polyethylene glycol (PEG) chains may be covalently linked to increase liposome stability and in vivo circulation time, a possibility that warrants further study.

Polymeric NPs

NPs are currently favored because of their controlled drug release properties. Among the various types of nano-loaded systems, polymeric NPs have received widespread interest in the field of medical biology for their high efficiency, ease of preparation, long-term circulation, biodegradability, low toxicity, and ability to absorb and carry other molecules, in contrast to other nano-sized drug carriers.^{26,41} Polymeric NPs can be roughly subdivided into chitosan, polylactic acid and other branches such as dendrimers and nanogels.

Chitosan

Chitosan (CS), a non-toxic mucoadhesive polymer with biocompatibility and sites for easy modification, has excellent biodegradability, and has been shown to be a reliable, valid intestinal permeation enhancer favoring the absorption of protein drugs.^{9,42} This natural polysaccharide made from crustaceans and insects has been widely applied in various drug delivery systems because of its biocompatibility, safety, and mucoadhesive properties.⁶ The achievement of glycemic control remains the most important therapeutic goal for preventing DN and other complications of diabetes, because chronic hyperglycemia is closely associated with microvascular inflammation.⁴³ Traditional blood glucose control methods, such as insulin administered subcutaneously, have been used as an invasive method to control glycemia in DN; its many drawbacks include needle phobia, pain, skin bulges, infections, hypoglycemia, peripheral hyperinsulinemia, and poor pharmacodynamics. Moreover, engineered formulations of oral insulin tend to have relatively poor absorption in the gastrointestinal tract.^{9,44} CS NPs thus provide a new avenue for oral insulin administration.

A derivative of CS known as trimethyl CS has superior solubility to that of CS.⁴⁵ Ghavimishamekh et al⁹ have collected trimethyl CS carrying insulin and demonstrated that, in rats, oral therapy with oral insulin-loaded trimethyl CS NPs decreases fasting blood glucose (FBG) to a similar extent as that after injection of insulin; oral administration of insulin-loaded trimethyl CS NPs clearly decreases serum TGF- β 1 levels, whereas subcutaneous insulin injection does not. This finding has been attributed to CS, as a natural cationic polysaccharide, facilitating mucosal adhesion and increasing absorption through the ionic interaction between its cationic amine groups and the anionic groups at the epithelial cell surface. Consequently, tight junctions of the intestinal epithelium temporarily open, thus supporting inter-epithelial insulin transport. The response of alginate to pH is reflected in that it dissolves in the alkaline pH of the intestine, but is much more stable under the acidic pH values of other organs, thus resulting in retention of insulin molecules in the gastrointestinal tract.^{6,9} When designing new formulations in future studies, considering the pH sensitivity of NPs is essential to identifying approaches for drug delivery systems, and avoiding significant washout of the drug after oral administration. As a non-toxic, biodegradable cationic polymer, CS is relatively immunogenic and

has especially good macro-adhesion that can prolong the presence of drugs in the GI tract. CS binds negatively charged insulin and forms polyanion NPs with a size of 210 nm; these features can overcome the short duration of subcutaneous insulin injection.^{46,47} Additionally, CS NPs' increased retention time, ultrafine size, and ability to release drugs for longer periods of time make them ideal oral delivery vehicles.⁴⁸ Asal et al⁴⁶ have used an emulsion solvent diffusion method to functionalize CS NPs (ChNPs) with poly lactic-co-glycolic acid (PLGA). They successfully fabricated CS gold NPs functionalized with poly lactic-PLGA (ChAuNP/PLGA). The zeta potential values for the prepared ChAuNPs decorated with PLGA changed from $+37 \pm 4.3$ to -26 ± 2.1 mv after loading with insulin, thus indicating the better stability of the NPs in the final product. The positive charge of Ch enables NPs to traverse cell membranes or facilitate endocytosis. Research has demonstrated that the pharmacological availability and bioavailability of orally administered insulin-loaded ChAuNP/PLGA are clearly higher than those of orally administered insulin solution. This nano-delivery method similarly promotes the sustained release of the drug. Traditional Chinese medicine is considered to have strong development potential for DN therapy, because of its lower adverse effects and higher safety than conventional insulin and MET therapy. Polydatin (resveratrol-3-O- β -mono-D-glucoside) is well known as a polypeptide NP with antiglycation, antioxidant, anti-inflammatory, and nephroprotective effects, which can be easily prepared from common sources such as peanuts, grapes, and red wine.⁴⁹⁻⁵¹ Abeer M. Abd El-Hameed have synthesized polydatin-loaded CS NPs (POL-NPs) through a modified ionotropic gelation method. The POL-NPs have been found to downregulate proinflammatory responses and mediators during the treatment of diabetes-associated complications.⁵² Notably, the hypoglycemic efficacy of POL-NPs is more pronounced than that of free POL. The mechanism of the renal protective effect of POL-NPs against DN involves regulating blood glucose and HbA1c by promoting insulin secretion, thus resulting in antidiabetic function; improving oxidative stress status and suppressing AGE formation, thus resulting in antioxidant and anti-inflammatory function; and improving the absorption and prolonged-release properties of NPs. POL-NP formulas substituting conventional hypoglycemic agents have received attention because of the protective roles of NPs loaded with traditional Chinese medicines in renal disease. Berberine (BBR), a natural isoquinoline alkaloid obtained from Chinese rhizomacoptidis, cortex phellodendri, berberis, and other types of plants, has a hypoglycemic effect through promoting insulin receptor expression, thus enhancing the sensitivity of the body to insulin; its hypoglycemic effect is similar to that of MET, the most commonly prescribed oral hypoglycemic agent.^{53,54} In addition, BBR also significantly ameliorates glucose metabolism and is therefore considered a promising anti-diabetic drug⁵⁵. P-glycoprotein (Pgp-mediated drug efflux combined with tight junctions in the intestines clearly prevents BBR across the intestinal epithelium. Given that CS has been described to facilitate paracellular drug transport through opening intercellular tight junctions, Xiong et al⁶ have synthesized and characterized Brij-grafted-CS (BC). They innovatively grafted Brij-S20 (polyethylene glycol octadecyl ether) onto the amino group of CS to reverse the Pgp-mediated drug efflux and found that BC12 (BC with 12% grafting) exhibits excellent drug loading capacity and encapsulation efficacy. Moreover, they have demonstrated that BBR-BC12-NPs greatly increase the oral absorption of BBR through promoting intestinal permeability by facilitating paracellular transport and inhibiting Pgp-mediated drug efflux. CS is expected to become one of the most promising drug delivery pathways in the future, because of its various functions, which deserve further research.

CS has a number of advantages in formulation development, including its biocompatibility, biodegradability, and low immunogenicity.⁵⁶ However, the low bioactivity and poor water solubility of CS may greatly limit its clinical application.⁵⁷ Some studies have indicated that chemical modification can enhance the properties of CS without losing its unique characteristics, thus enabling a wider range of applications.⁵⁸ Therefore, structural and functional modifications of CS to obtain different CS derivatives with good water solubility and bioactivity are a focus of research.

Polylactic Acid

Among biodegradable materials, polylactide or poly(lactic acid) are most commonly used, because they are derived from renewable resources such as sugar, corn or vegetables.⁵⁹ Polylactoses, such as poly (D, L-lactide) (PLA), PLGA, poly- ϵ -caprolactone, gelatin, CS, and gelatin poly (alkyl cyanoacrylates), as biodegradable polymeric NPs, have been widely used as a platform for controlled drug release delivery systems for a variety of diseases such as diabetes and other malignant diseases, as well as kidney tissue engineering, because of their low toxicity, biocompatibility, and biodegradability. Some nondegradable polymers tend to have the disadvantage of requiring removal after loss of insulin

effectiveness, eg, ethylene vinyl acetate.⁶⁰ Because of its longer duration of action than that of typical subcutaneous injection of free insulin, polylactose has gradually attracted attention as a sustained-release drug delivery system.

Xiong et al⁶¹ have attached PLA segments to both ends of a Pluronic P85 copolymer to generate an amphiphilic PLA-P85-PLA block copolymer. Vesicular NPs have been demonstrated to deliver hydrophobic drugs and hydrophilic drugs. Moreover, degradation products produced by PLA block copolymers can enter the tricarboxylic acid cycle or be eliminated through the kidneys.⁶² Insulin-loaded PLA-P85-PLA vesicles have been found to be used to maintain blood glucose homeostasis for longer than normal subcutaneous injection of free insulin. The mechanism of prolonging hypoglycemic effects may involve the following. 1. PLA-P85-PLA vesicles protect insulin against enzymatic degradation in the GI tract. 2. PLA-P85-PLA vesicles (178 nm) with suitable particle size are conducive to insulin absorption in the intestines. 3. P85, owing to its amphiphilic properties, shows high cell membrane permeability in the intestines. 4. The small size and amphiphilic characteristics of vesicles delay macromolecular transport across the intestinal epithelium of insulin-loaded PLA-P85-PLA vesicles.^{61,63} In addition to enhancing the bioavailability of insulin, the development of polylactose in certain herbal medicines has also been investigated, because chemical-based dosing regimens are not only complex to synthesize and costly, but also ineffective and have substantial toxic adverse effects on the human body. Studies have indicated that some Chinese herbs significantly decrease both structural damage and functional changes in DN, but clinical applications are severely hampered by their low solubility in water and poor bioavailability. A recent study has reported that *Tinospora cordifolia* contains antioxidants, radical scavengers, hepatoprotective agents, anticancer agents, antiallergics, immune modulators, and anti-inflammatory compounds.⁶⁴ *Tinospora cordifolia* (Willd.) has been used as an antihypertensive and anti-inflammatory therapeutic agent by Ambalavanand et al⁶⁵ for the synthesis of TC-PLA NPs through a double-emulsion solvent evaporation method. In rats treated with TC-PLA NPs, a significant decrease in the expression of inflammatory cytokines has been achieved, and inflammation and fibrosis in DN have been reported to be caused by ROS and pro-inflammatory cytokines. TC-PLA NPs effectively control DN by enhancing the active antioxidant function of plant components and decreasing their inflammation.^{65,66} Overall, TC-PLA NPs protected renal function mainly through decreasing levels of blood glucose, stabilizing renal parameters, decreasing levels of inflammatory cytokines, and regulating gene expression levels. Studies have also shed light on modern approaches to promote the development of traditional Chinese medicine. Although biodegradable polymers such as PLA are generally considered to be safe, their immunotoxicity should still not be neglected, because smaller NPs appear to result in more damage to normal cells.⁶⁷

Depending on the choice of polymer and method of nanocarrier fabrication and drug incorporation, polymeric nanocarriers constitute an important class of materials for biomedical applications.⁶⁸ However, the safety and effectiveness of polymeric nanocarriers in the human body have not yet been demonstrated in a systematic review, and high-grade evidence is still lacking. The next research steps should involve studying this aspect in greater detail.

Inorganic NPs

Inorganic NPs involve the application of inorganic or hybrid nanomaterials and nanosized objects in the field of molecular medicine, including imaging examinations, medical diagnosis, therapy, clinical research, and basic science. Inorganic NPs have been developed in various imaging applications leading to medical diagnosis, therapy, or combination therapy.^{61,69} Inorganic NPs generally consist of metal, silica, nano-oxides, nano-composite oxides, nanometals, or alloys.⁶⁹

Nano-Oxides

Inorganic nanomedicine has achieved innovative medical breakthroughs for biomarker discovery and molecular diagnostics. For example, iron oxide magnetic NPs (MNPs), composed of iron oxide NPs, have been found to improve the practicality and accuracy of magnetic resonance imaging, and have been approved for use as signal enhancers in tumor imaging and therapy.⁶⁹

Islet autoantibodies can be measured before the appearance of some clinical symptoms, thus indicating that DN is a predictable disease. Inspired by this finding, LOX-1 has been validated as a biomarker in early stages of DN and has been found to mediate a vast array of inflammatory changes in renal tissue.⁷⁰ Breil et al⁷¹ have synthesized anti-LOX

-1-ultrasmall superparamagnetic iron oxide PEG-coated NPs (USPIO-PEG NPs) to detect noninvasively inflammatory renal lesions in early stages of DN. In DN mice, the signal intensity has been found to significantly decrease in T2*-weighted cortical MR, but has not shown any changes in normal mice injected with anti-LOX-1 USPIOs or in DN mice injected with untargeted USPIO NPs.^{71,72} Renal LOX-1 upregulation is associated with lipid peroxidation stress, inflammation, and fibrosis. Activated macrophages expressing LOX-1 selectively accumulate LOX-1-targeted PEG-coated USPIO NPs simultaneously. Signal reduction induced by LOX-1-targeted USPIO administration has been demonstrated to reflect the inflammatory response—an important feature of early stage of DN. Li et al⁷³ have also noted that USPIO-PEG exhibits good cellular internalization and long-term MRI tracking properties. However, the lack of information regarding the safety and toxicity of LOX-1 targeted USPIOs in humans requires further investigation.^{71,74}

After the heart, the kidneys contain the second most mitochondria and have the second highest level of energy metabolism. The main function of mitochondria, the most susceptible organelles to oxidative damage, is to generate large amounts of ATP via OXPHOS, thus ensuring the operation of normal physiological kidney function.^{75,76} Mitochondrial dysfunction caused by hyperglycemia plays a role in promoting the development of DN. Altered energy metabolism or altered mitochondrial dysfunction in DN can lead to renal dysfunction and eventually CKD.⁷⁵ A dynamic balance between oxidative eustress and distress (ie, cellular redox homeostasis) is the basis for proper mitochondrial function. Biocompatible transition metal oxide NPs are highly sought after for their wide range of remarkable properties and applications, particularly their electron-donating and accepting activity, which is considered the best type of NP to maintain the balance of the redox potential of cellular mitochondria.⁷⁷ C-Mn₃O₄ NP has become one of the least expensive and most effective materials for oxidative stress, owing to its free radical scavenging activity and good biocompatibility. C-Mn₃O₄ NP is autocatalytic and has protective effects through preventing mitochondrial permeability transition pore (mPTP) opening and ATP depletion. C-Mn₃O₄ NP can reduce oxidative stress by controlling the redox homeostasis, while the functionalization of citric acid greatly increases its biocompatibility. Simultaneously the Mn²⁺ ions produce harmless free radicals and can be well controlled by biological systems. Thus, C-Mn₃O₄ NPs show favorable biological properties and low toxicity, and are novel nanoplatforams for anti-DN drugs.⁷⁸ Adhikari et al⁷⁷ have evaluated the potential of citrate functionalized Mn₃O₄ NPs (C-Mn₃O₄NPs) to alleviate mitochondrial injury and have indicated that C-Mn₃O₄ NPs protect mitochondria—the master regulator of cellular redox equilibrium, which promote high cell viability through scavenging of intracellular ROS, inhibit apoptotic triggers, and prevent loss of antioxidant enzymes (Figure 2). In vivo animal experiments have indicated that, according to drug elimination curve analysis of C-Mn₃O₄ NPs, the NPs in the blood of a CKD mouse model begin to be eliminated after 12 hours, or even after 24 hours in blood near the kidneys. Nanodrug concentrations in the therapeutic range are $0.95 \pm 0.09 \mu\text{g}^{-1}$. The above results suggest that C-Mn₃O₄ NPs eliminate ROS—signaling molecules that enhance cell growth—while maintaining persistent long-term release in the kidneys. More interestingly in mice, C-Mn₃O₄ NPs do not have any toxic side effects.⁷⁹ Given these advantages, C-Mn₃O₄ NPs may be superior to traditional oral hypoglycemic drugs.

Zinc oxide NPs (ZnO NPs), among the most abundant and functionally diverse metal oxide NPs, are widely used in biomedical purposes for anticancer, drug delivery, antibacterial, and diabetes treatment, and antiinflammation.⁸⁰ NPs made of ZnO are among the most important nanomaterials in this context, owing to their high electron mobility, good chemical stability, low toxicity, and biological compatibility.⁸¹ ZnO NPs regulate glucose levels through the following mechanisms: 1. decreasing glucose absorption by inhibiting the intestinal alpha-glucosidase enzyme, ameliorating hepatic glycogenesis by acting on insulin signaling pathways, and enhancing glycolysis, thereby improving glucose disposal; 2. a potential antiglycation effect through inhibition of AGE formation and prevention of changes in protein structure that may result from a consequence of covering of amino groups in protein structures or sequestration of the reacting group in glycation species by ZnO NPs; and 3. increasing Zn concentration, because strong antioxidants attenuate oxidative stress in diabetic rats.^{82–84} In diabetic kidneys, Alomari et al⁸⁵ have demonstrated that ZnO NP treatment not only suppresses the expression of TGF- β 1, collagen IV, and fibronectin, but also increases the expression of MMP-9, a key enzyme that downregulates the level of ECM and is associated with the occurrence and development of DN.^{66,85} Of note, the accumulation of Zn in kidney tissues and the development of toxicity must be avoided, which requires the regulation of the dose of the drug to the organism within a strict safety threshold.⁸⁶

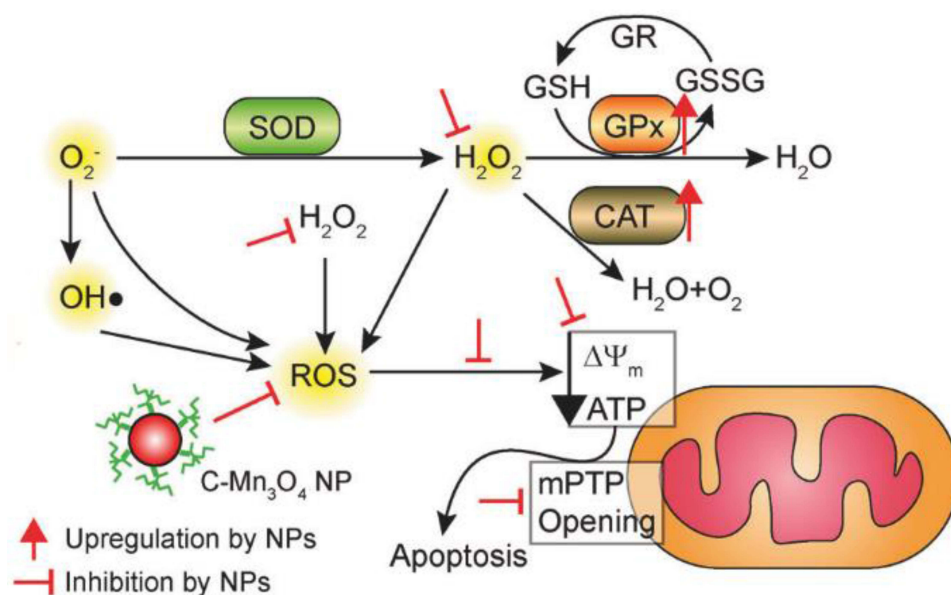


Figure 2 Schematic diagram of the pathway by which C-Mn₃O₄ NPs maintain redox homeostasis by counteracting H₂O₂ distress.

Notes: Adapted from Adhikari A, Mondal S, Chatterjee T et al, Redox nanomedicine ameliorates chronic kidney disease (CKD) by mitochondrial reconditioning in mice. *Commun Biol.* 2021;4(1): Article 1013⁷⁷.

Abbreviation: C- Mn₃O₄ NPs, citrate functionalized Mn₃O₄ nanoparticles.

Nano-Composite Oxides

Drug-loaded NPs tend to unload drugs either slowly or prematurely while circulating in the bloodstream at the target tissues; thus, slow unloading effects are expected.⁸⁷ Nano-composite oxides are a new type of functional material widely used in many industries, including chemical, medical, and electronics applications.⁸⁸ The pathogenesis of DN often does not occur through a single pathway, and nanocomposites have gradually received attention because of their superior characteristics to simultaneously combat multiple pathogenesis.

The reducing activity of antioxidant enzymes combined with enhanced free radical generation and lipid peroxidation are major causative factors in CKD.⁸⁹ Antioxidant therapy plays an important role in patients with diabetes, whereas traditional antioxidants, such as vitamins E and C, do not appear helpful.⁹⁰ Zhong et al⁹¹ have designed hollow mesoporous silica nanocomposite (HMSN) particles doped with trace cerium oxide. In contrast to the poor safety of organic and inorganic NPs, such as potential carcinogenicity, statistically significant chronic toxicity has not been observed for small non-porous silica nanocomposites (SNPs) and MSNPs.^{91,92} The authors aimed to construct an oxidative stress-targeted multifunctional nanocomposite, fabricated by doping with trace cerium oxide to achieve long-term cyclic scavenging of free radicals in the body. CeO₂ provides high oxygen storage abilities and enhances redox properties.⁹³ The hollow structure of silica was etched to hold MET. In vitro drug release studies of MET from MET-HMSN-CeO₂ NPs developed by Zhong et al have indicated that, at 24 hours, only 40% of the total drug is released from MET-HMSN-CeO₂ NPs, thus implying sustained release of MET. The authors have observed the apoptosis of NRK-52E cells with TUNEL assays; the changes in HG-induced apoptosis of NRK-52E cells were ameliorated by treatment with MET-HMSN-CeO₂ NPs. Thus, the results also demonstrated that HMSN-CeO₂ NPs can achieve long-term cyclic scavenging of free radicals in vivo. Additionally, the antioxidative effect of cerium loaded HMSN occurs in vivo, as observed in pathological detection. Such nanocomplexes are used to treat DN by controlling hypoglycemia, inhibiting oxidative stress, and improving renal apoptosis, thereby also providing ideas and application prospects for treating other diseases with multiple pathogenic mechanisms.

Nanometals and Nanoalloys

During the new millennium, NPs of noble metals such as silver, gold, and platinum have been developed in medical and pharmaceutical applications; these NPs have received extensive attention in biomedicine, such as CKD treatment,

because of their easy synthesis and stability in long-term storage.^{94,95} Nanoparticle preparations of metals have advantages of stability, lower dosages, easy storability, and sustained availability, which surpass the low mechanical properties of polymeric NPs. However, heavy metals are difficult to remove by biodegradation, and heavy metal NPs often accumulate in the kidneys.⁹⁶ Therefore, how to avoid the adverse effects caused by heavy metals to the greatest extent possible has become a focus of current nanoparticle research.

For example, gold NPs (AuNPs) are metal NPs ranging in size from 2 to 100 nanometers.⁹⁷ AuNPs are commonly used in medical molecular diagnosis and treatment and drug delivery, and the chemical modification of AuNPs can decrease toxicity.^{98,99} To overcome the limitation of ionic gold easily inactivated by complexation, Alomari et al¹⁰⁰ have used a modified sodium citrate approach to synthesize 50 nm AuNPs, which have long blood circulation times.¹⁰¹ Under high glucose, TGF- β 1 is released from glomerular mesangial cells, thus initiating epithelial-mesenchymal transition (EMT) and the accumulation of ECM proteins, an important characteristic of early DN, and driving renal fibrosis. TGF- β 1 is linked to glomerular sclerosis, loss of podocytes, and DN.^{102–104} In a DN mouse model induced by STZ, AuNPs have been found to decrease TGF- β 1 mRNA and protein levels, thereby decreasing ECM proteins, collagen IV, and fibronectin. These results indicate that AuNPs maintain the integrity and permeability of the glomerular filtration barrier through limiting mesangial matrix expansion and ameliorating podocyte damage in the diabetic condition.⁹⁹ In another study, Manna et al⁹⁵ have demonstrated that peel extract-stabilized gold nanoparticles (PPE-AuNPs) inhibit rage-induced hyperactivation of NOX-4/p47phox, thereby decreasing ROS production by inhibiting protein glycation and dephosphorylating the MAPK/NF- κ B/Stat3-mediated proinflammatory response (Figure 3). Some studies have shown that pomegranate peel extract (PPE) inhibits lipid peroxidation in vivo and has antioxidant effects on removing ROS.¹⁰¹ In addition, exosomal urinary microRNAs protected by RNase activity have gradually become an accurate new biomarker for the early diagnosis of CKD, in which metal nanoparticle-based diagnosis is playing an increasingly important role.¹⁰⁵ Tan et al¹⁰⁶ have reported a sensor consisting of AuNPs and a composite under an aptamer panel to detect cancer biomarkers for cancer diagnosis. Compared with expensive qRT-PCR miRNA detection kits, the AuNP detection method is simple, economical, and low-tech, and does not require complex equipment or trained personnel to detect the expression of microRNAs.^{5,107} Nossier et al⁵ have used a simple AuNP colorimetric assay to diagnose DN; the test solution is red because the miRNA-probe adsorbs on AuNPs, thus preventing salt-induced aggregation of AuNPs. When non-specific miRNAs are present, only short probe molecules are adsorbed on AuNPs, and the test solution is blue. The assay's sensitivity for detecting miRNAs is comparable to that of qRT-PCR, but the NPs are less expensive and easier to use. Furthermore, silver NPs are most commonly used, owing to their high antimicrobial activity.¹⁰⁸ Olalekan et al¹⁰⁹ have synthesized bitter melon NPs that significantly upregulate SOCS3 expression in STZ-induced diabetic rats, thereby downregulating the JAK/STAT signaling pathway and inhibiting its activation. This cascade of signaling is associated with the proliferation of mesangial cells. The NPs significantly upregulate the expression of PTEN in non-treated diabetic rats. The PTEN gene, a negative regulator of the PI3K/Akt pathway, visibly alleviates the inflammatory response, although the DNA damage and mutations easily caused by the properties of nanomaterials limit clinical use.¹¹⁰ Silver ions can easily cause DNA damage and mutation, thus limiting its clinical application. However, creatinine is the most important indicator in DN and is often used as a sub-index for DN to assess renal insufficiency in clinical practice. Silver ions can be used in in vitro biological tests of creatinine levels.¹¹¹ Olalekan et al¹¹² have used polyvinyl alcohol (PVA) and polyvinyl pyrrolidone (PVP) to modify silver NPs, whose color is related to the concentration of creatinine in the solution, and blood creatinine content can be quickly measured by an image processing system (colorimetry). Thus, PVP-coated silver NPs (AgNPs@PVP) and PVA-coated silver NPs (AgNPs@PVA) are expected to be applied in clinical settings to detect creatinine concentration in patients in the near future.

Quantum Dots

Quantum dots (QDs) are luminescent NPs that have been used extensively in QD displays and in a variety of bioimaging procedures.¹¹³ Although the pathogenesis of DN is complex, QD NPs are developing into a new research field for diseases such as DN.^{114–116}

The polyethylene glycol coated QDs described by Pollinger et al¹¹⁴ prolong drug release time in the circulatory system and can also be enriched in the renal mesangium for targeted therapy. In addition, to overcome the limitations of traditional immunohistochemical detection of multiple biomarkers, Liu et al¹¹⁷ have established a dual-color

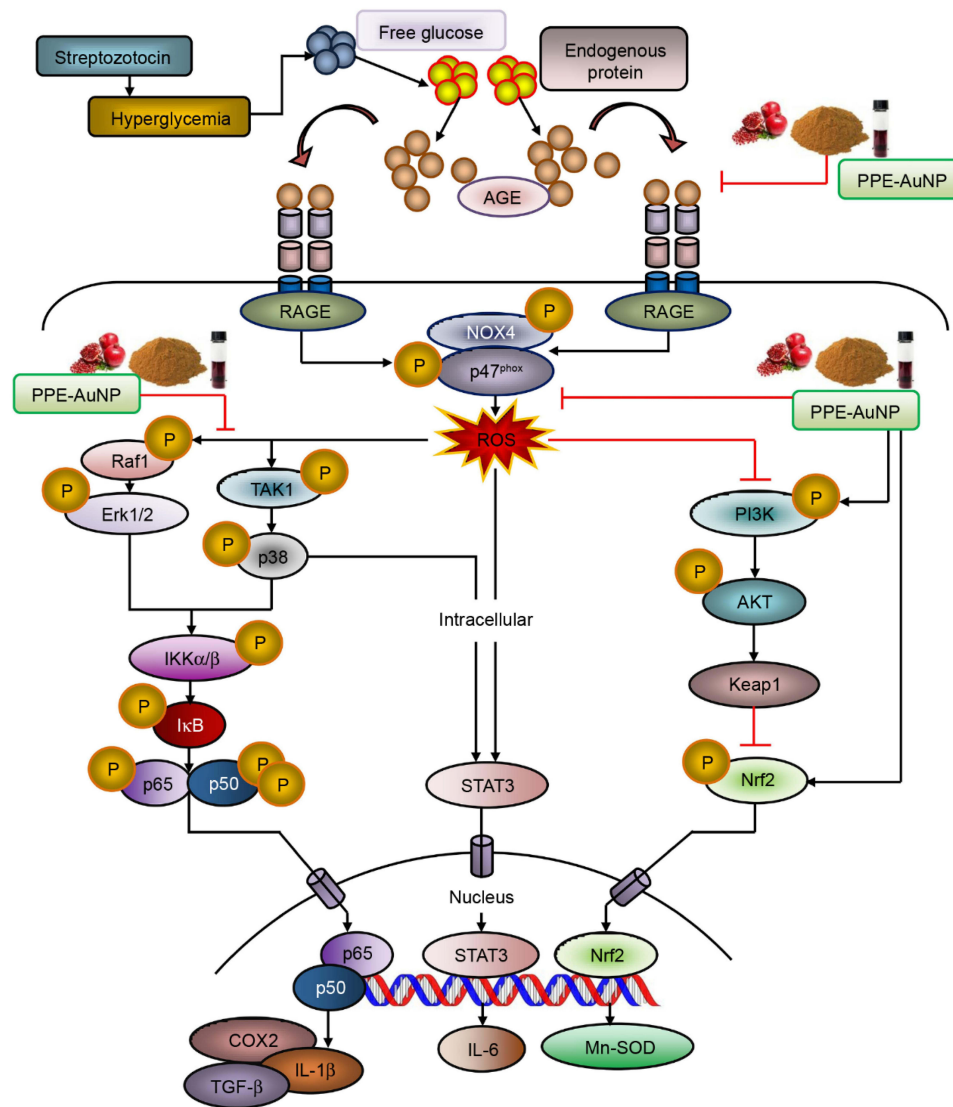


Figure 3 The diagram illustrates the possible potential pathways of action of PPE-AuNP in reversing STZ-induced DN.

Notes: Reproduced from Manna K, Mishra S, Saha M et al. Amelioration of diabetic nephropathy using pomegranate peel extract-stabilized gold nanoparticles: assessment of NF-kappaB and Nrf2 signaling system. *Int J Nanomedicine*. 2019;14:1753–1777⁹⁵.

Abbreviations: AuNP, gold nanoparticle; PPE, pomegranate peel extract; STZ, streptozotocin; DN, Diabetic nephropathy.

immunofluorescence labeling technology for the application of QD primary antibody probes. Recognizing and binding Aldose reductase (AR) and Toll-like receptor 4 (TLR4), the linked probe QDs can yield stable and strong fluorescence and provide clearer imaging. However, the application of dual-color immunofluorescence labeling with QD cell therapy requires enhanced efficiency of conjugating QDs with the primary Ab. Therefore, further study is warranted.

Although nanotechnology has become increasingly dependent on QDs, as a result of increasing concerns regarding toxicity and chemical instability, QDs have been restricted to long-term usage.¹¹⁸ Two strategies are currently used to decrease the cytotoxicity of QDs, including the use of an aqueous synthesis method, as well as the formation of core/shell QDs at the core to protect against oxidation.¹¹⁹ We hope that in the future, more effective ways to further reduce the toxicity of QDs will be identified.

Biological NPs

Biomimetic nanomedicine is a bioengineered preparation that combines the physicochemical properties of various functional materials and the advantages of biomaterials, especially mammalian cells and pathogens (such as viruses)

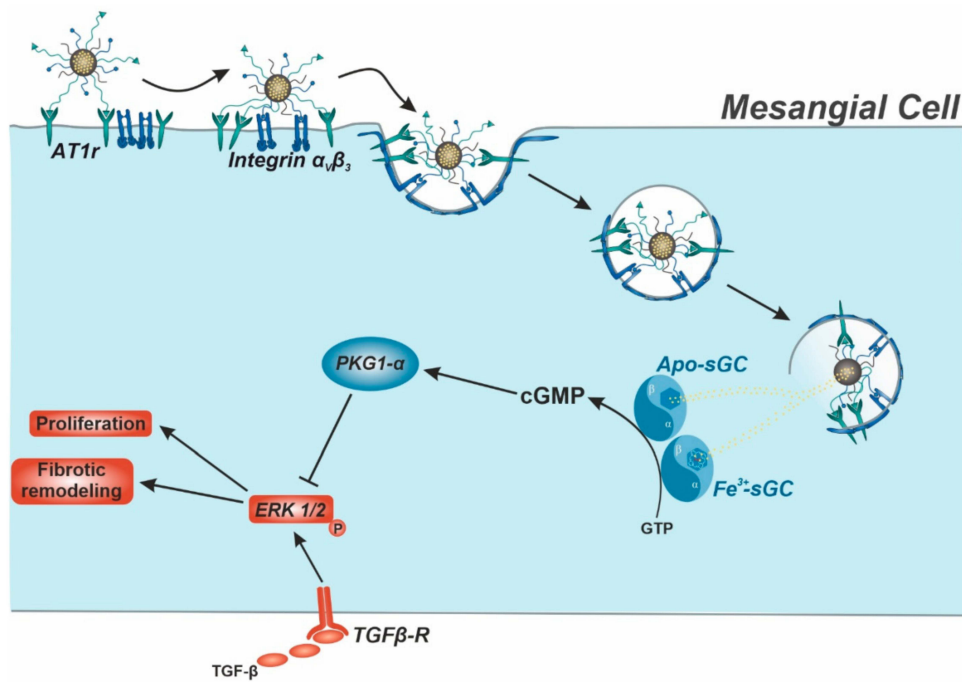


Figure 4 Schematic diagram of treatment principle. Nanoparticle (NP)-assisted cinaciguat (CCG) delivery to intracellular Apo-/Fe³⁺-sGC of target mesangial cells.

Notes: After a sequential and thereby highly cell-selective mesangial NP uptake, CCG is released into the cytosol due to endolysosomal degradation of the NP. Here, CCG binds and thus activates both oxidized and heme-free sGC, leading to an increased production of 30.50-cyclic guanosine monophosphate (cGMP) and a protein kinase I α (PKG1- α) mediated inhibition of transforming growth factor β (TGF- β)-induced pathological remodeling. Adapted from Fleischmann D, Harloff M, Figueroa SM, Schlossmann J, Goeperich A. Targeted Delivery of Soluble Guanylate Cyclase (sGC) Activator Cinaciguat to Renal Mesangial Cells via Virus-Mimetic Nanoparticles Potentiates Anti-Fibrotic Effects by cGMP-Mediated Suppression of the TGF-beta Pathway. *Int J Mol Sci.* 2021;22(5):2557¹²⁴.

Abbreviation: sGC, the soluble form of guanylate cyclase.

in biomaterials are the most commonly used components for synthesizing NPs with good properties. Its biocompatibility and high accumulation capacity are becoming a promising therapeutic approach.¹²⁰ Compared with traditional biomedical nanomaterials, viral nanomaterials, as biological nanomaterials, can integrate the nucleic acid of the virus into the nucleic acid of the host cell, with higher specificity and stronger targeting specificity.^{121–123} Figueroa et al¹²⁴ used influenza A virus Nps, which drives cinaciguat (CCG) (degraded by endolysosomes) into renal mesangial sites. CCG from the cytoplasm can specifically bind and activate the soluble form of guanylate cyclase (sGC), which then converts guanosine triphosphate (GTP) to 30.50-cyclic guanosine monophosphate (cGMP), thereby downregulating excessive glomerular fibrosis (Figure 4).^{124,125} The results showed that the same therapeutic effect was achieved despite only 10% of the administered dose carried by NPs compared to free ccg concentrations, and the drug delivery system appeared to significantly reduce the biological toxicity of the carried drug. In a word, particles with mimetic virus triploidy as a more accurate and stable recognition strategy showed better efficacy than traditional NPs.¹²³ How to solve the biotoxicity of bio-nano drug-loaded particles and their degradation products is still one of the main challenges in the clinical application of nano-biomedicine, which deserves further research.

Challenges and Future Perspectives

DN has evolved into a major condition in type 1 and type 2 diabetes worldwide. It is a complicated disorder, and given that the number of people with diabetes is increasing, the incidence of DN is expected to soar. Currently, the goal of halting DN progression and achieving regression of albuminuria focuses on glucose, blood pressure, and lipid control, which remain standard therapy for DN. Oral hypoglycemic drugs, such as MET, often aggravate kidney damage through adverse reactions.¹²⁶ The molecular targets of DN are crucial for site-specific targeted delivery, and future studies are expected to increasingly focus on drug delivery systems based on NPs. NPs can eliminate the toxicity characteristics of

oral drugs, such as short duration of action, low oral bioavailability, and toxic adverse effects, thus providing new effective, and feasible therapeutic strategies for DN treatment.

Early DN often does not show any clinical symptoms. Because it is a progressive nephropathy, early detection and treatment of DN is particularly recommended. However, routine clinical examinations for DN, such as renal biopsy, are invasive and this histopathologic examination are considered for only patients with clinical presentation or disease progression.¹²⁷ Therefore, new NP-based methods may offer a new approach to the diagnosis of DN, such as the use of lox-1-targeted iron oxide NPs for non-invasive imaging of DN. Renal damage is often key for the early diagnosis of DN. However, cells are susceptible to programmed cell death when large amounts of iron accumulate, and small NPs are associated with greater cytotoxicity.¹²⁸ When the toxicity of iron ions is overcome, we believe that NPs such as lox-1-targeted iron oxide NPs will have bright prospects.

Multiple factors and mechanisms leading to DN interact and develop together, such as vasoactive pathways, including alterations in the renin-angiotensin-aldosterone system, hypertrophy of mesangial and tubular epithelial cells, endothelin receptor-mediated DN progression, and metabolic pathways, including the generation of ROS, activation of PKC, advanced glycation end products, and polyol pathways, and the release of transcription factors such as NF- κ B. Therefore, treating a single disease pathway with a single drug may not be sufficient to produce a therapeutic effect. Polymer-carrier NPs may play an important role in overcoming the renal filtration threshold, because their low molecular weight allows them to be filtered through the kidneys and retained in the kidneys through post-glomerular processes. In addition, MET-HMSN-CeO₂, as a multifunctional NPs, and MET interacts with CeO₂, thus forming aggregates, enhancing antioxidant activity of MET, and protecting the kidneys by enhancing resistance to cellular death. This approach unequivocally addresses the problem of the single hypoglycemic effect of MET and additionally shows potential effects leading to apoptotic resistance. Therefore, other properties of multifunctional NPs deserve further exploration. From a synergistic therapy perspective, these approaches may present new therapeutic opportunities to treat complex heterogeneous diseases.¹²⁹ However, nanocarriers for therapeutic purposes must be safe *in vivo*, which requires that the concentration of silica be kept within safety limits.

As discussed previously, research on innovative nano-drug delivery platforms has begun, but further exploration in DN is needed to assess the pharmacokinetics and pharmacodynamics of characteristic proteinuria in pathological conditions, as well as changes in the GFR in pathological conditions, and to design an optimal intrarenal drug delivery platform to treat DN.^{130,131} Among the numerous NPs, biological NPs, such as those mimicking the sequence recognition strategy of influenza A virus, tend to be more kidney specific, thereby increasing their bioavailability. Unfortunately, little research has been performed on the application of viral NPs as drug delivery vehicles. Furthermore, evaluating the toxicity and biosafety of viral NPs requires extended trials, and *in vitro* and *in vivo* studies. DN therapy requires high renal drug concentrations, thus necessitating the development of concentration-dependent targeted drug delivery systems, such as peptides, CS, and other nanoplatforms.

Compared with other DN treatments, the aim of nanoplatform-based drug delivery is to deliver drugs precisely to kidney sites and inhibit multiple pathogenic pathways. The application of multifunctional targeted NPs in DN diagnosis is a development trend whose successful clinical translation will require long-range action and safety assessment through *in vitro* and *in vivo* studies. In DN NP drug development, drug-loaded NPs are modified on the basis of the directional properties of DN pathological mechanisms, thereby increasing the interaction of nanodrugs with renal cells, and improving the intracellular growth of GBM epithelial cells, podocytes, mesangial cells, and proximal tubule cells. The development of nano-drug delivery platforms provides higher drug efficacy and safety, as well as new precise therapeutic measures to treat patients with DN.

Abbreviations

DN, Diabetic nephropathy; CKD, chronic kidney disease; DM, diabetes mellitus; T1DM, type 1 DM; T2DM, type 2 DM; ECM, extracellular matrix; LNs, lipid nanoparticles; NPs, nanoparticles; STZ-NA, streptozotocin-nicotinamide; PCL-PEI, polycaprolactone-polyethyleneimine; KTP, kidney-targeting peptide; RH, rhein; KLPPR, kidney-targeted RH-loaded liponanoparticles with a yolk-shell structure composed by PCL-PEI-based cores and KTP-modified lipid layers; SLN, Solid lipid nanoparticle; MET, metformin; PEG, Polyethylene glycol; CS, chitosan; FBG, fasting blood glucose;

ChnPs, CS NPs; PLGA, poly lactic-co-glycolic acid; ChAuNP/PLGACS gold NPs functionalized with PLGA; POL-NPs, polydatinloaded CS NPs; BBR, Berberine; BC, Brij-grafted-CS; BC12, BC with 12% grafting; Pgp, P-glycoprotein; Brij-S20, Polyethylene glycol octadecyl ether; PLA, poly D, L-lactide; PLA-P85-PLA, PLA segments to both ends of a Pluronic P85 copolymer to generate an amphiphilic vesicles; TC, *Tinospora cordifolia*; TC-PLA NPs, TC-PLA nanoparticles; MNPs, magnetic nanoparticles; USPIO-PEG NPs, ultrasmall superparamagnetic iron oxide PEG-coated NPs; C- Mn₃O₄NPs, citrate functionalized Mn₃O₄ nanoparticles; ROS, reactive oxygen species; ZnO NPs, Zinc oxide NPs; RAGE, receptor of advanced glycation end-products; HMSN, hollow mesoporous silica nanocomposite; AuNPs, Gold NPs; EMT, epithelial-mesenchymal transition; QDs, quantum dots; AR, Aldose reductase; TLR4, Toll-like receptor 4; CCG, cinaciguat; SGc, soluble form of guanylate cyclase; GTP, guanosine triphosphate; cGMP, cyclic guanosine monophosphate; PVP, Polyvinyl pyrrolidone; PVA, Polyvinyl alcohol; AgNPs@PVP, PVP-coated silver nanoparticles; AgNPs@PVA, PVA-coated silver nanoparticles; PPE-AuNP, peel extract-stabilized gold nanoparticle.

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Previously reported data were used to support this study and are available at DOI. These prior studies (and datasets) are cited at relevant places within the text as references.

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Disclosure

The authors declare that they have no conflicts of interest.

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