Mechanisms of Chinese Herbal Medicines for Diabetic Nephropathy Fibrosis Treatment

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Abstract
Diabetic nephropathy (DN) is a severe microvascular complication of diabetes mellitus that is one of the main causes of end-stage renal disease, causing considerable health problems as well as significant financial burden worldwide. The pathological features of DN include loss of normal nephrons, massive fibroblast and myofibroblast hyperplasia, accumulation of extracellular matrix proteins, thickening of the basement membrane, and tubulointerstitial fibrosis. Renal fibrosis is a final and critical pathological change in DN. Although progress has been made in understanding the pathogenesis of DN fibrosis, current conventional treatment strategies may not be completely effective in preventing the disease's progression. Traditionally, Chinese herbal medicines (CHMs) composed of natural ingredients have been used for symptomatic relief of DN. Increasing numbers of studies have confirmed that CHMs can exert a renoprotective effect in DN, and antifibrosis has been identified as a key mechanism. In this review, we summarize the antifibrotic efficacy of CHM preparations, single herbal medicines, and their bioactive compounds based on their effects on diminishing the inflammatory response and oxidative stress, regulating transforming growth factor, preventing epithelial-mesenchymal transition, and modulating microRNAs. We intend to provide patients of DN with therapeutic interventions that are complementary to existing options.

Key words: Chinese herbal medicines, diabetic nephropathy, renal fibrosis, signaling pathway

INTRODUCTION

Diabetic nephropathy (DN) is the leading cause of end-stage renal disease (ESRD), and its incidence is increasing annually, placing a heavy burden on healthcare systems worldwide.¹ DN is characterized by loss of normal nephrons, massive fibroblast and myofibroblast hyperplasia, accumulation of extracellular matrix (ECM) proteins, thickening of the basement membrane, and tubulointerstitial fibrosis (TIF).² Renal fibrosis resulting from DN is usually considered irreversible, and its pathogenesis is not well understood. Emerging research suggests that inflammatory reactions, oxidative stress (OS), transforming growth factors, epithelial-mesenchymal transition (EMT), and microRNAs are closely related with this process. The recommended therapeutic regimens for renal fibrosis have been derived from experimental studies based on controlling elevations in blood glucose, blood pressure, and blood lipids,
as well as the reduction of urinary albumin. However, there is currently no single therapy that can completely alleviate renal fibrosis. Novel interventions that can effectively delay the progression of renal fibrosis are therefore urgently needed.

Chinese herbal medicines (CHMs) have long been used to treat DN in China. CHMs have several advantages over standard medical treatments for the prevention of DN due to their lower toxicity or fewer side effects. In recent years, many investigations have revealed that attempts to treat DN with CHMs have achieved some efficacy. In this review, we will discuss the clinical efficacy of CHMs and their bioactive compounds in the treatment of renal fibrosis, as well as the mechanisms and molecular targets of these CHMs elucidated by experimental and clinical studies.

**ANTI-INFLAMMATION**

Advanced glycation end products (AGEs) play an important role in the development of DN. AGEs can thicken and distort membranes, which is caused by covalent collagen crosslinks. AGEs also stimulate matrix production and mesangial proliferation by maintaining high glucose (HG) levels. The receptor for AGEs (RAGE) is a pattern recognition receptor found on variety of cell membranes. Overexpression and activation of RAGE amplify cellular perturbation in hyperglycemia-affected tissues such as the kidney and large blood vessels. Augmented AGE deposition in the vasculature, as well as excessive AGE-RAGE interactions, activates intracellular signaling cascades, resulting in a variety of proinflammatory and profibrotic cellular responses via multiple downstream pathways. Inflammatory cells, such as macrophages and monocytes, and proinflammatory molecules, such as Toll-like receptors (TLRs), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), monocyte chemoattractant protein-1, intercellular adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM-1), may be released. These proinflammatory cytokines are key regulators of fibrosis and are significantly related to proteinuria and glomerular basement membrane thickening. Various Chinese medicines, including formula preparations and single herbs or their active ingredients, can ameliorate renal fibrosis in DN by inhibiting inflammation [Figure 1].

Arabinogalactan (AG), isolated from Angelica sinensis, exhibits anti-inflammatory activities. NF-κB activation has been found to be elevated in diabetic rats, which leads to sustained release of inflammatory cytokines. Therefore, RAGE-NF-κB is a key signaling pathway that mediates the progression of DN. The phosphorylation of NF-κBp65 is significantly suppressed in diabetic kidneys, and the expression of inflammatory cytokines regulated by NF-κB, such as TGF-β1, TNF-α, IL-1, and IL-6, is reduced following AG treatment. Furthermore, AG may block RAGE-NF-κB signaling via AGEs antagonism. The interaction between AG and RAGE can halt the over-proliferation of glomerular mesangial cells by diminishing the NF-κB activation. Jowiseungki decoction, which is composed of three herbs (rhubarb, mirabilitum, and licorice), also prevents inflammation-induced renal fibrosis via the downregulation of NF-κB. Qi-dan-di-huang, which is composed of Astragalus, Salvia miltiorrhiza, Radix Rehmanniae, Chinese yam, and licorice, can inhibit the NF-κB pathway, decreasing the expression of inflammatory mediators, reducing glycogen and protein deposition in DN, and preventing renal fibrosis. Furthermore, the G-protein-coupled bile acid receptor Gpbar1 (TGR5) inhibits the NF-κB signaling pathway. Gentipicoside, the main active secoiridoid glycoside of Gentiana manshurica Kitagawa, downregulates the TGR5-β/NF-κB signaling pathway to ameliorate the pathological progression of diabetic renal fibrosis.

Bupleurum polysaccharides (BPs), which are derived from the root of Bupleurum smithii var. parvifolium, exert anti-inflammatory and antioxidant effects. The therapeutic effectiveness of BPs in suppressing inflammatory reactions might be linked to modulation of the TLR4 signaling pathway. TLRs are portrayed as a type of pattern recognition receptors that recognize pathogen-associated molecular patterns (PAMPs) and damage associated molecular patterns (DAMPs) and thus participate in innate immune reactions against infection and injury. TLRs are expressed on both antigen-presenting cells and intrinsic kidney cells. The stimulation of TLR signaling induces polarization and infiltration of M1 macrophages and intervenes with the transcription of NF-κB and the subsequent inflammatory cascade, which releases proinflammatory cytokines and chemokines. Thus, activation of the TLR signaling pathway exacerbates renal fibrosis by aggravating inflammation. Paeoniflorin, which is isolated from the dried root of Paeonia lactiflora Pall., could decrease urinary albumin excretion and inhibit macrophage infiltration by blocking TLR2/4 signaling pathway. In addition, high-mobility group box 1 (HMGB1), which can be passively released by cells damaged by diabetes, is an endogenous ligand of TLR4. The release of HMGB1 can be induced by hyperglycemia, which causes tubulointerstitial inflammation during the progression of DN. Some recent studies have also found that HMGB1 might promote inflammation by interacting with TLR4 and activating its downstream signaling pathways. HMGB1 can also activate NF-κB and secrete proinflammatory cytokines such as IL-6, IL-1β, and TNF-α, by interacting with its receptors. These proinflammatory responses result in the accumulation of fibronectin in the
fibrosis process. Liu et al. found that the expression of HMGB1 and TLR4 in mouse kidneys is decreased following BP treatment. Treatment with BPs can inhibit the activity of the HMGB1-TLR4 signaling pathway, decreasing the activity of NF-κB and the levels of inflammatory cytokines such as IL-6 and TNF-α. In addition, recent studies have indicated that the nucleotide-binding oligomerization domain (Nod)-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome, an IL-1β family cytokine-activating protein complex, can be activated in type 2 diabetes mellitus and its renal complications. Huangkui capsule can alleviate renal tubular EMT in DN model rats by suppressing NLRP3 inflammasome activation and TLR4/NF-κB signaling, and it is well acknowledged that EMT is a significant process in the early stage of renal interstitial fibrosis (RIF). Some studies have demonstrated that both diabetic rodent models and patients with DN exhibit macrophage infiltration in the glomerulus and tubulointerstitium. In addition, the degree of infiltration is positively correlated with RIF in patients with DN. Following the activation of inducible nitric oxide synthase (iNOS), a substantial amount of nitric oxide, a hallmark of macrophage activation, is produced. Liao et al. demonstrated that Chinese medicines can protect against diabetic nephropathy fibrosis via inhibiting inflammation by blocking NF-κB, TLR-2/4, and HMGB1/TLR4 signaling pathways and activating TGR5.
demonstrated that Huangqi alleviated DN by regulating macrophage iNOS activity. Taken together, the results indicate that CHM protects against immune-inflammatory pathological injury by regulating the release of proinflammatory molecules or mediating their upstream or downstream pathways.

ANTIOXIDATION

OS is marked by a notable overproduction of reactive oxygen species (ROS) and reactive nitrogen species. OS is a major cause of renal fibrosis, which frequently results in ESRD. OS is also associated with inflammatory cell recruitment, which increases inflammation by stimulating the release of cytokines such as IL-1, IL-18, and TNF-α. In patients with diabetes, hyperglycemia upregulates the most important resource of ROS, nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (Nox) in intrinsic renal cells. The enhanced expression of Nox4 may directly result in excessive ROS production and indirectly exacerbates OS through Nox4-mediated uncoupling of endothelial nitric oxide synthase. Moreover, macromolecule oxidative products such as malondialdehyde (MDA), 8-hydroxy-2-deoxyguanosine, and oxidative carbonyl proteins are elevated in the kidney. The main source of ECM deposition in the tubulointerstitium during fibrosis is myofibroblasts expressing α-smooth muscle actin (α-SMA). Nox is a well-known mediator that promotes the transition of fibroblasts to myofibroblasts, leading to an increase in ECM synthesis and worsening of renal fibrosis. Simultaneously, the activity of antioxidant enzymes such as superoxide dismutase (SOD) is usually decreased in the diabetic state.

Lycium chinense (family Solanaceae) is a well-known CHM. Some studies have shown that Lycium chinense leaf extract markedly increases the activities of antioxidant enzymes, while reducing MDA levels, confirming its antioxidant properties. Nuclear factor erythroid-derived 2-related factor 2 (Nrf2) plays a significant positive role in the system of OS defense and is linked to renal disease progression. Nrf2 modulates heme oxygenase-1 (HO-1), an important antioxidant enzyme. In response to various stimuli, HO-1 reduces the ROS levels in cells. As a result, activating Nrf2 is considered a therapy for preventing DN progression. Tetrandrine (Tet), a bisbenzylisoquinoline alkaloid, is isolated from the roots of Stephania tetrandra. Su et al. demonstrated that Tet could significantly restrain renal damage by upregulating the expression of p-Nrf2 and HO-1. Ho et al. demonstrated that curcumin can prevent ECM accumulation in DN by alleviating HG-induced superoxide. Nepeta angustifolia (NA) is a vital medicinal plant that is used in a variety of traditional Chinese medicine (TCM) prescriptions. In vitro studies with H₂O₂-treated mesangial cells (MCs) revealed that NA exerts a considerable effect on reducing cell damage and OS, thereby inhibiting the development of diabetic renal fibrosis. Not only single herbs or their active ingredients, but also formula preparations, have a therapeutic effect on OS. A study demonstrated that Liuwei Dihuang pill (LDP) exerts protective effects on the function of MCs and ameliorates the progression of renal fibrosis by increasing SOD and NOS, decreasing MDA concentrations, and preventing lipid peroxidation-induced damage. In summary, CHM prevents OS pathological injury by balancing OS indicator levels through multicomponent and multitarget mechanisms.

MODULATION OF TRANSFORMING GROWTH FACTORS

Under hyperglycemia, renal cells release a variety of growth factors, including TGF-β1, angiotensin II, and platelet-derived growth factor, and all these factors influence the progression of diabetic kidney disease (DKD). The TGF family includes three isoforms: TGF-β1, TGF-2, and TGF-3. Abnormal activation of TGF-β and its receptors, as well as the downstream signaling pathways, can result in increased ECM accumulation and decreased degradation, thereby causing renal fibrosis. TGF-β and TGF-β receptors are expressed in virtually all types of renal cells and play a role in the onset and progression of DN renal fibrosis via autocrine and paracrine pathways. In both experimental animal models and human kidney disorders, TGF-β1 causes fibrogenesis by stimulating the downstream Smad signaling pathway. TGF-β1 can also build a signaling network with other non-Smad-dependent signaling pathways, such as pp60c-src, epithelial growth factor receptor (EGFR), mitogen-activated protein kinase (MAPK), p53, and PI3K/AKT to promote the expression of genes associated with renal fibrosis. It has been reported that TGF-β1 promotes Smad3 to induce fibrosis, whereas the overexpression of Smad7 inhibits fibrosis in the kidney.

In recent years, an increasing body of evidence has supported the notion that TGF-β1 levels are elevated in both DN mice and patients with DN. Chaihuang-Yishen granule (also called Qilong-Lishui granule) is manufactured based on the TCM theory for the treatment of DKD and blocks TGF-β1/Smad3-mediated renal fibrosis to attenuate DN. Hu et al. demonstrated that treatment with rhein, an extract of the Chinese herb rhubarb, significantly reduces the level of TGF-β1 in animals with DN. Taxus chinesis, belonging to the Taxaceae family, can suppress the TGF-β1/Smad signaling pathway in DN rats by reducing the expression of TGF-β1 and α-SMA and the phosphorylation of Smad2 and Smad3. Peroxisome proliferator-activated receptor (PPAR) activation
mitigates aldosterone-induced mitochondrial dysfunction in podocytes.\(^{165}\) Huangqi Decoction, composed of seven herbs (Astragalus, Poria, Trichosanthes, Ophiopogon, Schisandra, Licorice, and Rehmannia), ameliorates DN by regulating TGF-β1/MAPK/PPAR-γ signaling.\(^{166}\) Artemisinin (ATZ) is obtained mostly from the Artemisia annua (Asteraceae).\(^{167}\) ATZ suppresses TGF-β1 protein expression in kidney tissues while simultaneously activating the Nrf2 signaling pathway and increasing antioxidant protein expression to reduce early renal OS damage in DN rats, resulting in protective effects on DN kidneys.\(^{168}\) Baicalin, a main bioactive component of Scutellaria baicalensis, has traditionally been widely used to treat DN and can attenuate ECM via the TGF-β1/Smad3 pathway.\(^{169}\) Berberine, extracted from Rhizoma coptidis, reduces the increase in the protein and mRNA expression levels of TGF-β, vimentin, and α-SMA in DN rats.\(^{170}\) Li et al.\(^{171}\) showed that acetylsalicycillin, the main ingredient of Zicao, reduces TGF-β1 expression and Smad2/3 phosphorylation while increasing Smad7 expression. Additionally, in vitro treatment significantly reduces plasminogen activator inhibitor type 1, collagen III and IV, and Smad-2/3 phosphorylation induced by TGF-β1 in HK2 immortalized human proximal tubule epithelial cells. These studies suggest that CHM may protect against diabetic renal fibrosis by regulating the autocrine and paracrine TGF pathways, and TGF modulation may be used as a potential treatment for patients with diabetic renal fibrosis.

**REGULATION OF EMT**

EMT is one of the initiating factors in the development of TIF.\(^{172}\) The tight junctions between cells are destroyed during the EMT process. The intercellular tight junction protein E-cadherin, for example, could be downregulated, causing cells to transition into mesenchymal cells. Following that, renal tubular epithelial cells (TECs) leave renal tubules and enter the interstitium via the disrupted basement membrane. The epithelial cells of the renal tubulointerstitium transform into myofibroblasts expressing α-SMA.\(^{173}\) Moreover, under HG conditions, the key components of Notch2 signaling in normal rat kidney cell clone 52E (NRK-52E) cells are depleted or overexpressed during EMT in renal tubular cells. Licorice is one of the most commonly used herbs in TCMs. The licorice extract could suppress HG-mediated EMT in NRK-52E cells primarily by inhibiting the Notch2 pathway.\(^{174}\) Ruan et al.\(^{175}\) reported that phenolic compounds from Mori Cortex inhibit EMT caused by sodium olate-induced lipid deposition in NRK-52E cells through CD36. Studies have suggested that p38 MAPK may play a crucial role in HG-induced EMT by activating activator protein 1 in TECs.\(^{176}\) Cordyceps sinensis is a prevalent component in TCM for the treatment of DN. The major active components are nucleosides and nucleobases, which inhibit EMT accumulation by regulating p38 MAPK signaling pathways.\(^{177}\) β-catenin is a transcriptional coactivator in the Wnt/β-catenin signaling pathway, which hastens EMT development in podocytes.\(^{178}\) Sun et al.\(^{179}\) demonstrated that inhibition of the Wnt/β-catenin signaling pathway may be one of the potential mechanisms by which curcumin prevents EMT of podocytes in streptozotocin-induced diabetic rats [Figure 2]. Autophagy is generally considered as a significant self-defense mechanism for protecting cells from stress responses such as OS, DNA damage, and endoplasmic reticulum stress.\(^{180}\) A study revealed that treatment with DKD mouse serum reduces autophagy, resulting in increases in EMT and apoptosis. Tripterygium glycoside is a TCM extract with anti-fibrotic effects that can protect against EMT by enhancing autophagy.\(^{181}\) Astragaloside IV (AS-IV), one of the bioactive saponin extracts of Astragalus root, may also exert effects on podocyte EMT by activating autophagy.\(^{182}\) During the EMT process, the expression of some antifibrotic regulators, such as inhibitor of differentiation 2 (Id2), is decreased.\(^{183}\) The loss or reduction of E-cadherin is the most significant change observed during EMT, and Twist can inhibit its expression, leading to maintenance of the interstitial state and EMT.\(^{84-86}\) Xiao et al.\(^{187}\) established that oxymatrine, which is extracted from the root of Sophora flavescens, can reverse EMT by binding Id2 to Twist and reducing Twist’s ability to regulate downstream target genes. In brief, CHM can exert regulatory effects against EMT to ameliorate renal fibrosis through several signaling pathways, autophagy, and cell mediators. EMT in kidneys can be utilized as a novel route and potential pharmacological target for the treatment of DN.

**MODULATION OF MIRNAS**

MicroRNAs (miRNAs) are endogenous noncoding RNAs with a length of 20–22 nucleotides that regulate gene expression by binding to the 3′-untranslated regions of mRNA targets.\(^{88-89}\) Studies have suggested that miRNA dysregulation may induce disruptions in podocyte homeostasis and the accumulation of ECM proteins linked to fibrosis and glomerular dysfunction.\(^{90-92}\) Thus, abnormal expression of miRNAs may play an important role in the onset and progression of diabetic renal fibrosis. Several miRNAs are overexpressed in DN, while others are reportedly downregulated in patients with DN.\(^{93}\) For example, miR-192 induces fibrosis in human renal TECs by targeting glucagon-like peptide-1 receptor (GLP-1R), which plays a vital positive regulatory role in diabetic renal fibrosis.\(^{94-95}\) Icariin alleviates tubulointerstitial fibrosis through a novel mechanism of downregulating miR-192 and upregulating GLP-1R expression.\(^{96}\) A recent study has revealed that miR-21 enhances RIF by regulating the TGF-β1/Smad pathway-induced EMT in proximal
**Figure 2:** CHMs attenuate renal fibrosis in diabetic nephropathy by regulating TGF and inhibiting EMT through suppressing Notch2, Wnt/β-catenin, p38 MAPK signaling pathway. It is reported that some CHMs contribute to reductions in TGF-β1 expression and Smad2/3 phosphorylation and increases in Smad7 expression. CHM, Chinese herbal medicines; TGF, transforming growth factor; MAPK, Mitogen-activated protein kinase; NICD2, cleaved Notch2; EMT, epithelial-mesenchymal transition; α-SMA, α-smooth muscle actin.

TECs.\(^{[97]}\) AS-IV ameliorates renal fibrosis by blocking miR-21 overexpression, which induces podocyte dedifferentiation and MC activation.\(^{[98]}\) Spleen-Kidney Supplemetning Formula, which is composed of six herbs (Radix Astragali, Fructus Corni, Rhizoma Coptidis, Cortex Mori, Radix Puerariae Lobatae, and Herba Eupatorii), considerably reduces the expression level of plasma miR-21, thereby attenuating renal fibrosis and protecting renal function.\(^{[99]}\) miR-155-5p is highly expressed in renal tissues of patients with DN, and its expression level increases with disease progression.\(^{[100]}\) Dihydromyricetin inhibits miR-155-5p expression in NRK-52E cells, resulting in reduced DN-induced RIF development in vitro and in vitro.\(^{[101]}\) However, in many studies, miRNA induces a protective mechanism against DN. miR-423-5p has been shown to play a therapeutic role in HG-mediated podocyte injury. By targeting nicotinamide adenine dinucleotide phosphate oxidase 4, upregulation of miR-423-5p expression can reduce OS, apoptosis, and inflammatory reactions.\(^{[102]}\) Hou et al.\(^{[103]}\) found that apigenin could ameliorate unusual downregulation of miR-423-5p in an in vitro DN model. In summary, CHM could alleviate fibrosis and protect kidney function by regulating the expression of miRNAs, thereby presenting a novel treatment opportunity for DN.

**CONCLUSION**

Numerous experimental and clinical studies have examined the effectiveness of CHM in the treatment of renal fibrosis. Due to their satisfactory clinical efficacy, the use of CHMs is a suitable strategy for the treatment and management of diabetic renal fibrosis. The renoprotective effects of CHM can be demonstrated through multiple pathways, including alleviating inflammation, attenuating OS, regulating TGFs, decreasing EMT, and modulating miRNAs. Some studies
Table 1: Researches on the mechanisms of single CHM and/or monomers in the treatment of diabetic nephropathy fibrosis

| Name                          | Origins           | Targets                                           | Mechanisms                                      | Ref.           | Publication year |
|-------------------------------|-------------------|---------------------------------------------------|-------------------------------------------------|----------------|------------------|
| Arabinoglanuc                  | Angelica sinensis | NF-κBp65, TGF-β1, TNF-α, IL-1, IL-6, RAGE-NF-κB signaling pathway | Anti-inflammation and regulation of TGFs         | Sui et al.     | 2018             |
| Gentiopicroside                | Gentiana manshurica Kitagawa | TGR5, NF-κB                                      | Anti-inflammation                               | Xiao et al.    | 2020             |
| Huangkui capsule               | Abelmoschus manihot | NLRP3, TLR4/NF-κB signaling                        | Alleviation of renal tubular EMT and inflammation reactions | Han et al.     | 2019             |
| Astragaloside IV               | Radix Astragali   | iNOS activity of macrophages, miR-21, mesangial cell, autophagy | Anti-inflammation, attenuation of EMT, regulation of TGFs and miRNAs | Liao et al.     | 2017             |
| Lycium chinense leaf extract   | Solanaceae        | GSH, SOD, CAT, MDA, TNF-α, IL-6, IL-1β            | Antioxidative stress and inflammation           | Olatunji et al.| 2018             |
| Tetrandrine                    | Stephania tetandra | p-Nrf2, HO-1                                      | Antioxidative stress                            | Su et al.      | 2020             |
| Curcumin                      | Rhizoma Curcuma longae | Superoxide, Wnt/β-catenin signaling pathway | Preventing ECM accumulation and oxidative stress, attenuating EMT | Ho et al.       | 2016             |
| Nepeta angustifolia           | Schizonepeta tenuifolia Briq. | SOD, ROS, MDA                                   | Reducing cell damage and oxidative stress       | Huang et al.   | 2020             |
| Rhein                         | Rhus barba        | TGF-β1                                            | Regulation of TGFs                              | Hu et al.      | 2019             |
| Taxus chinensis               | Taxaceae          | TGF-β1, α-SMA, Smad2, Smad3                       | Regulation of TGFs                              | Hong-Bo et al. | 2018             |
| Artemisinin                   | Artemisia annua   | TGF-β1, Nrf2                                      | Antioxidative stress and regulation of TGFs     | Zhang et al.   | 2020             |
| Baicalin                      | S. baicalensis    | TGF-β1/Smad3 signaling pathway                    | Attenuation of ECM and regulation of TGFs      | Zheng et al.   | 2020             |
| Acetylsphikorin                | Arnebia euchroma  | TGF-β1, Smad2/3, Smad7, PAT-1, Collagen III and IV | Regulation of TGFs and reduction of fibrosis proteins | Li et al.      | 2018             |
| Licorice extract              | Glycyrrhiza       | Notch2 signaling pathway, NRK-52E cells            | Attenuation of EMT                              | Hsu et al.     | 2020             |
| Mori Cortex                   | Morus alba L      | NRK-52E cells, CD36                               | Attenuation of EMT                              | Ruan et al.    | 2021             |
| Cordyceps                     | Cordyceps sinensis | p38 MAPK signaling pathway                      | Attenuation of EMT                              | Dong et al.    | 2019             |
| Tripterygium glycoside         | Tripterygium wilfordii | Autophagy                          | Attenuation of EMT                              | Tao et al.     | 2021             |
| Oxymatrine                    | Sophora flavescens | Id2, Twist                                       | Attenuation of EMT                              | Xiao et al.    | 2020             |
| Icarin                        | Herba epimedi     | MIR-192, GLP-1R                                 | Regulation of miRNAs                           | Jia et al.     | 2021             |
| Dihydromyricetin              | Ampelopsis Michx  | MIR-155-5p, NRK-52E cells                        | Regulation of miRNAs                           | Guo et al.     | 2019             |
| Apigenin                      | Celery            | MIR-423-5p                                       | Regulation of miRNAs                           | Hou et al.     | 2021             |

CHM: Chinese herbal medicine, NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells, TGF: transforming growth factor, TNF: tumor necrosis factor, IL: interleukin, RAGE: receptor for advanced glycation end products, TGR5: G-protein-coupled bile acid receptor Gpbar1, TLR4: Toll-like receptor 4, HMGB1: high-mobility group box 1, NLRP3: nucleotide-binding oligomerization domain (Nod)-like receptor family pyrin domain-containing 3, iNOS: inducible nitric oxide synthase, GSH: glutathione, SOD: superoxide dismutase, CAT: catalase, MDA: malondialdehyde, p-Nrf2: p-nuclear factor erythroid-derived 2-related factor 2, HO-1: heme oxygenase-1, ROS: reactive oxygen species, iNOS: inducible nitric oxide synthase, EMT: epithelial-mesenchymal transition, ECM: extracellular matrix, α-SMA: α-smooth muscle actin, MAPK: mitogen-activated protein kinase, PAI-1: plasminogen activator inhibitor type 1, NRK-52E: normal rat kidney cell clone 52E, Id2: inhibitor of differentiation 2, MiR: microRNAs, GLP-1R: glucagon-like peptide-1 receptor.
pertaining to the mechanisms of single CHM or monomers and formula preparations are summarized in Table 1 and Table 2, respectively. The signaling pathways and molecular targets implicated in the mechanisms underlying the renoprotective properties of CHM may include NF-κB, TGF-β/Smad, and Wnt/β-catenin. However, although there are many studies proving the beneficial effects of CHMs on DN, most of them are small. Before CHM can be used as a primary treatment in DN, more well-designed and properly conducted clinical trials with large sample sizes are required to establish its efficacy and safety. We believe that the use of CHMs in the onset and progression of diabetic renal fibrosis is a promising new treatment option, as demonstrated by our study.

Conflicts of interest
None declared.

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REFERENCES
1. El Ghoul B, Daaboul Y, Korjian S, El Alam A, Mansour A, Hariri E, et al. Etiology of End-Stage Renal Disease and Arterial Stiffness among Hemodialysis Patients. Biomed Res Int 2017;2017:1-6.
2. Kanwar YS, Sun Y, Liu X, Liu FY, Chen S. A glimpse of various pathogenetic mechanisms of diabetic nephropathy. Annu Rev Pathol 2011;6:395-423.
3. Lim AKH. Diabetic nephropathy - complications and treatment. Int J Nephrol Renovasc Dis 2014;7:361-81.
4. Tong XL, Dong L, Chen L, Zhen Z. Treatment of diabetes using traditional Chinese medicine: past, present and future. Am J Chin Med 2012;40: 877-86.
5. Shi X, Lu XG, Zhan LB, Qi X, Liang LN, Hu SY, et al. The effects of the Chinese medicine ZiBu PiYin recipe on the hippocampus in a rat model of diabetes-associated cognitive decline: a proteomic analysis. Diabetologia 2011;54:1888-99.
6. Zhao HL, Sun Y, Qiao CF, Ye CK, Leung RK, Tsui SK, et al. Sustained antidiabetic effects of a berberine-containing Chinese herbal medicine through regulation of hepatic gene expression. Diabetes 2012;61: 933-43.
7. Wen X, Zeng Y, Liu L, Zhang H, Xu W, Li N, et al. Zhenqing recipe alleviates diabetic nephropathy in experimental type 2 diabetic rats through suppression of SREBP-1c. J Ethnopharmacol 2012;142:144-50.
8. Li YQ, Liu XM, Zhang MM, Ma JX. Systematic review of TCM published in Chinese journals/study of current status of Meta-analysis. Chin. J. Evidence Based Med 2007;7:180–8.
9. Goldin A, Beckman JA, Schmidt AM, Creager MA. Advanced glycation end products: sparking the development of diabetic vascular injury. Circulation 2006;114:597-605.
10. Hudson BI, Lippman ME. Targeting RAGE Signaling in Inflammatory Disease. Annu Rev Med 2018;69:349-64.
11. Senatus LM, Schmidt AM. The AGE-RAGE Axis: Implications for Age-Associated Arterial Diseases. Front Genet 2017;8:187.

Table 2: Researches on the mechanisms of CHM formula preparations in the treatment of diabetic nephropathy fibrosis

| Formula                  | Composition                                      | Targets          | Mechanisms                   | Ref.          | Publication year |
|--------------------------|--------------------------------------------------|------------------|------------------------------|--------------|-----------------|
| Jowiseungki decoction    | Rhubarb, Mirabilitum, Licorice                   | NF-κB            | Anti-inflammation            | Meng et al.  | 2020            |
| Qi-dan-di-huang          | Astragalus, Salvia militia-rhiza, Radix Rehmanniae, Chinese yam, licorice | NF-κB pathway    | Anti-inflammation            | Ma et al.    | 2019            |
| Liuwei Dihuang pill      | Rehmannia glutinosa, Cornus, Yam, Cortex moutan, Rhi-zoma alismatis, Tuckahoe | SOD, NOS, MDA    | Antioxidative stress and protection of the function of mesangial cells | Xu et al.    | 2017            |
| Chaihuang-Yishen granule | Astragalus, Pyrospia, Angelica sinensis, Bupleurum, Rhizoma Dioscoreae Nipponicae, Polyporus, Leeches | TGF-β/Smad3 signaling pathway | Regulation of TGFs          | Zhao et al.  | 2014            |
| Huangqi Decoction        | Astragalus, Poria, Trichosanthes, Ophiopogon, Schisandra, Licorice, Rehmannia | TGF-β1, MAPK, PPAR | Regulation of TGFs           | Han et al.   | 2017            |
| Spleen-Kidney Supplemen-ting Formula | Radix Astragali, Fructus Corni, Rhizoma Coptidis, Cortex Morii, Radix Puerariae Lobatae, Herba Eupatorii | MiR-21           | Regulation of miRNAs         | Tian et al.  | 2018            |

CHM: Chinese herbal medicine, NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells, TGF: transforming growth factor, SOD: superoxide dismutase, NOS: nitric oxide synthase, MDA: malondialdehyde, MAPK: mitogen-activated protein kinase, PPAR: peroxisome proliferator-activated receptor, MiR: microRNAs.
12. Yang WJ, Li YR, Gao H, Wu XY, Wang XL, Wang GN, et al. Protective effect of the ethanol extract from Ligusticum chuanxiong rhizome against streptozotocin-induced diabetic nephropathy in mice. J Ethnopharmacol 2018;227:166-75.

13. Chen J, Hou XF, Wang G, Zhong QX, Liu Y, Qiu HH, et al. Terpene glycoside component from Moutan Cortex ameliorates diabetic nephropathy by regulating endothelial reticulum stress-related inflammatory responses. J Ethnopharmacol 2016;193:433-44.

14. Han WB, Ma Q, Liu YL, Wu W, Tu Y, Huang L, et al. Huangkui Capsule alleviates renal tubular epithelial-mesenchymal transition in diabetic nephropathy via inhibiting NLRP3 inflammasome activation and TLR4/NF-kB signaling. Phytotherapy Research 2019;57:203-14.

15. Dalla VM, Mussap M, Gallina P Bruseghin M, Cernigoi AM, Saller A, et al. Acute-phase markers of inflammation and glomerular structure in patients with type 2 diabetes. J Am Soc Nephrol 2005;16:S78-82.

16. Cao W, Li XQ, Liu L, Wang M, Fan HT, Li C, et al. Structural analysis of water-soluble glucans from the root of Angelica sinensis (Oliv.) Diels. Carbohydr Res 2006;341:1870-7.

17. Bierhaus A, Humpert PM, Marcos M, Wendt T, Chavakis T, Arnold B, et al., Understanding RAGE, the receptor for advanced glycation end products. J Mol Med 2005;83:876-86.

18. Sui Y, Liu W, Tian W, Li XQ, Cao W. A branched arabinoglucan from Angelica sinensis ameliorates diabetic renal damage in rats. Phytother Res 2019;33:818-31.

19. Meng X, Ma J, Kang SY, Jung HW, Park YK. Jowiseungki decoction affects diabetic nephropathy in mice through renal injury inhibition as evidenced by network pharmacology and gut microbiota analyses. Chin Med 2020;15:24.

20. Ma F, Li L, Wang Q, Chen Z, You Y, Gao P, et al. Qi-dan-di-huang decoction alleviates diabetic nephropathy by inhibiting the NF-kappaB pathway. Front Biosci 2019; 24:1477-86.

21. Xiao H, Sun X, Liu R, Chen Z, Lin Z, Yang Y, et al. Gentioseptide increases the bile acid receptor Gpbar1 (TGR5) to repress NF-kappaB pathway and ameliorate diabetic nephropathy. Pharmacol Res 2020;151:104559.

22. Xu H, Zhang Y, Zhang J, Chen D. Isolation and characterization of an anti-complementary polysaccharide D3-S1 from the roots of Bupleurum smithii. Int Immunopharmacol 2007;7:175-82.

23. Pan L, Weng H, Li H, Liu Z, Xu Y, Zhou C, et al. Therapeutic Effects of Bupleurum Polysaccharides in Streptozotocin Induced Diabetic Mice. PLoS One 2015;10:e0133212.

24. Wu J, Zhang YY, Guo L, Li H, Chen DF. Bupleurum polysaccharides attenuates lipopolysaccharide-induced inflammation via modulating Toll-like receptor 4 signaling. PLoS One 2013;8:e78051.

25. Usha P, Carol P. The role of toll-like receptors in diabetic kidney disease.Curr Opin Nephrol Hypertens 2018;27:30-40.

26. Zhang TM, Zhu QJ, Shao YX, Wang K, Wu YG. Paeonol prevents TLR2/4-mediated inflammation in type 2 diabetic nephropathy. Biosci Trends 2017;11:308-18.

27. Han WB, Ma Q, Liu YL, Wu W, Tu Y, Huang L, et al. Huangkui Capsule alleviates renal tubular epithelial-mesenchymal transition in diabetic nephropathy via inhibiting NLRP3 inflammasome activation and TLR4/NF-kB signaling. Phytotherapy Research 2019;57:203-14.

28. Zhang T, Zhu Q, Shao Y, Wang K, Wu Y. Paeonol prevents TLR2/4-mediated inflammation in type 2 diabetic nephropathy. Biosci Trends 2017;11:308-18.

29. Ma J, Chadban SJ, Zhao CY, Chen X, Kwan T, Punchapatkesan U, et al., TLR4 activation promotes podocyte injury and interstitial fibrosis in diabetic nephropathy. PLoS One 2014;9:e97985.

30. Wang Y, Zhong J, Zhang X, Liu Z, Yang Y, Gong Q, et al. The Role of HMGB1 in the Pathogenesis of Type 2 Diabetes. J Diabetes Res 2016;2016:2543268.

31. Kim J, Sohn E, Kim CS, Jo K, Kim JS. The role of high-mobility group box-1 protein in the development of diabetic nephropathy. Am J Nephrol 2011;33:524-9.

32. Yu M, Wang H, Ding A, Golenbock DT, Latz E, Czura CJ, et al. HMGB1 signals through toll-like receptor (TLR) 4 and TLR2. Shock 2006;26:174-79.

33. Liu ZZ, Weng HB, Zhang LJ, Pan LY, Sun W, Chen HX, et al. Bupleurum polysaccharides ameliorated renal injury in diabetic mice associated with suppression of HMGB1-TLR4 signaling. Chin J Nat Med 2019;17:641-9.

34. Han W, Ma Q, Liu Y, Wu W, Tu Y, Huang L, et al. Huangkui capsule alleviates renal tubular epithelial-mesenchymal transition in diabetic nephropathy via inhibiting NLRP3 inflammasome activation and TLR4/NF-kB signaling. Phytotherapy Research 2019;57:203-14.

35. Loeffer I, Wolf G. Epithelial-to-Mesenchymal Transition in Diabetic Nephropathy: Fact or Fiction? Cells 2015;4:631-52.

36. Tesch GH. Diabetic nephropathy - is this an immune disorder? Clin Sci 2017;131:2183-99.

37. Pena OM, Pistolic J, Raj D, Fjell CD, Hancock RE. Endotoxin tolerance represents a distinctive state of alternative polarization (M2) in human mononuclear cells. J Immunol 2011;186:7243-54.

38. Liao H, Hu L, Cheng X, Wang X, Li J, Banbury L, et al. Are the Therapeutic Effects of Huangqin (Astragalus membraneaus) on Diabetic Nephropathy Correlated with Its Regulation of Macrophage iNOS Activity? J Immunol Res 2017;2017:3780572.

39. Sedeek M, Nasrallah R, Touyz RM, Hébert RL. NADPH oxidases, reactive oxygen species, and the kidney: friend and foe. J Am Soc Nephrol 2013;24:1512-8.

40. Turkmen K. Inflammation, oxidative stress, apoptosis, and autophagy in diabetes mellitus and diabetic kidney disease: the Four Horsemen of the Apocalypse. Int Urol Nephrol 2017;49:837-44.

41. Elmarakby AA, Sullivan JC. Relationship between oxidative stress and inflammatory cytokines in diabetic nephropathy. Cardiovasc Ther 2012;30:49-59.

42. Wan C, Wu H, Zhang C. Role of NADPH oxidase in metabolic disease-related renal injury:an update. Oxid Med Cell Longev 2016;2016:7813072.

43. Lee DS, Wauquier F, Eid AA, Roman LJ, Ghosh-Choudhury G, Khazim K, et al. Nox4 NADPH oxidase mediates peroxynitrite-dependent upregulation of endothelial nitric-oxide synthase and fibronecin expression in response to angiotensin II: role of mitochondrial reactive oxygen species. J Biol Chem 2013;288:28668-86.

44. Sen S, Chen SL, Peng BA, Wu XY, Lui E, Chakrabarti S. Preventive effects of North American ginseng (Panax quinquefolium) on diabetic nephropathy. Phytomedicine 2012;19:49e505.

45. Bondi CD, Manickam N, Lee DY, Abboud HE, et al. NAD(P)H oxidase mediates TGF-beta1-induced activation of kidney myofibroblasts. J Am Soc Nephrol 2010;21:93-102.

46. Olatunji OJ, Chen H, Gorin Y, Abboud HE, et al. Protective effects of Ginkgo biloba against streptozotocin-induced diabetic nephropathy in mice. Phytomedicine 2012;20:1145-51.

47. Copple IM. The Keap1-Nrf2 defense pathway a promising therapeutic target? Adv Pharmacol 2012;63:43-79.

48. Zheng H, Whitman SA, Wu W, Wondrak GT, Wong PK, Fang D, et al. Therapeutic potential of Nrf2 activators in streptozotocin-induced diabetic nephropathy. Diabetes 2011;60:3055-66.

49. Liu T, Liu X, Li W. Tetradsrine, a Chinese plant-derived alkaloid, is a potential candidate for cancer chemotherapy. Oncotarget 2016;7:40800-15.

50. Su L, Cao P, Wang H. Tetradsrine mediates renal function and redox...
homeostasis in a streptozotocin-induced diabetic nephropathy rat model through Nrf2/HO-1 reactivation. Ann Trans Med 2020;8:990.

51. Ho C, Hsu YC, Lei CC, Mau SC, Shih YH, Lin CL. Curcumin Rescues Diabetic Renal Fibrosis by Targeting Superoxide-Mediated Wnt Signaling Pathways. Am J Med Sci 2016;351:286-95.

52. Huang S, Tan M, Guo F, Dong L, Liu Z, Yuan R, et al. Nepeta angustifolia C. Y. Wu improves renal injury in HFD/STZ-induced diabetic nephropathy and inhibits oxidative stress-induced apoptosis of mesangial cells. J Ethnopharmacol 2020;255:112771.

53. Xu ZJ, Shu S, Li ZJ, Liu YM, Zhang RY, Zhang Y. Liuwei Dihuang pill treats diabetic nephropathy in rats by inhibiting TGF-β/SMADs, MAPK, and NF-kB and upregulating expression of cytoglobin in renal tissues. Medicine 2017;96:e5879.

54. Meng XM, Nikolic-Paterson DJ, Lan HY. TGF-β: the master regulator of fibrosis. Nat Rev Nephrol 2016;12:325-38.

55. Hu HH, Chen DQ, Wang YN, Feng YL, Cao G, Vaziri ND. New insights into TGF-β1 expression prevents and high expression exacerbates diabetic nephropathy in mice. Proc Natl Acad Sci U S A 2015;112:5815-20.

56. Samarakoon R, Dobberfuhl AD, Cooley C, Overstreet JM, Patel S, Hathaway CK, Gasim AM, Grant R, Chang AS, Kim HS, Madden VJ, et al. Low TGFβ1 expression prevents and high expression exacerbates diabetic nephropathy in mice. Proc Natl Acad Sci U S A 2015;112:5815-20.

57. Xu ZJ, Shu S, Li ZJ, Liu YM, Zhang RY, Zhang Y. Liuwei Dihuang pill treats diabetic nephropathy in rats by inhibiting TGF-β/SMADs, MAPK, and NF-kB and upregulating expression of cytoglobin in renal tissues. Medicine 2017;96:e5879.

58. Meng XM, Nikolic-Paterson DJ, Lan HY. TGF-β: the master regulator of fibrosis. Nat Rev Nephrol 2016;12:325-38.

59. Ho C, Hsu YC, Lei CC, Mau SC, Shih YH, Lin CL. Curcumin Rescues Diabetic Renal Fibrosis by Targeting Superoxide-Mediated Wnt Signaling Pathways. Am J Med Sci 2016;351:286-95.

60. Hu HH, Chen DQ, Wang YN, Feng YL, Cao G, Vaziri ND. New insights into TGF-β1 expression prevents and high expression exacerbates diabetic nephropathy in mice. Proc Natl Acad Sci U S A 2015;112:5815-20.

61. Zhang H, Qi S, Song Y, Ling C. Artemisinin attenuates early renal damage on diabetic nephropathy rats through suppressing TGF-β1 regulator and activating the Nrf2 signaling pathway. Life Sci 2020;256:117966.

62. Zheng XP, Nie Q, Peng J, Fan XY, Jin YL, Chen G, et al. Kidney-targeted baicalin-lysozyme conjugate ameliorates renal fibrosis in rats with diabetic nephropathy induced by streptozotocin. BMC Nephrol 2020;21:174.

63. Li Z, Zhang W. Protective effect of berberine on renal fibrosis caused by diabetic nephropathy. Mol Med Rep 2017;16:1055-62.

64. Li Z, Hong Z, Peng Z, Zhao Y, Shao R. Acetylshikonin from Zicao ameliorates renal dysfunction and fibrosis in diabetic mice by inhibiting TGF-β1/Smad pathway. Hum Cell 2018;31:199-209.

65. Loeffler I, Wolf G. Epithelial-to-Mesenchymal Transition in Diabetic Nephropathy: Fact or Fiction? Cell 2015;4:631-52.

66. Singh M, Yelle N, Venugopal C, Singh SK. EMT: Mechanisms and therapeutic implications. Pharmacol Ther 2018;182:80-94.

67. Hsu YC, Chang PJ, Tung CW, Shih YH, Ni WC, Li YC, et al. De-Glycyrrhizinated Licorice Extract Attenuates High Glucose-Stimulated Renal Tubular Epithelial-Mesenchymal Transition via Suppressing the Notch2 Signaling Pathway. Cells 2020;9:125.

68. Ruan Y, Yuan PP, Wei YX, Zhang Q, Gao LY, Li PY, et al. Phenolic Compounds from Mori Cortex Ameliorate Sodium Oleate-Induced Epithelial-Mesenchymal Transition and Fibrosis in NRK-52E Cells through CD36. Molecules 2021;26:6133.

69. Lv ZM, Wang Q, Wan Q, Lin JG, Hu HY, Liu YX, et al. The role of the p38 MAPK signaling pathway in high glucose-induced epithelial-mesenchymal transition of cultured human renal tubular epithelial cells. PLoS One 2011;6:e22806.

70. Dong Z, Sun Y, Wei G, Li S, Zhao Z. A Nucleoside/Nucleobase-Rich Extract from Cordyceps Sinensis Inhibits the Epithelial-Mesenchymal Transition and Protects against Renal Fibrosis in Diabetic Nephropathy. Molecules 2019;24:4119.

71. K. Wu Z, Xue S, Zheng B, Ye R, Xu G, Zhang S, et al. Kidney-targeted baicalin-lysozyme conjugate ameliorates renal fibrosis in rats with diabetic nephropathy induced by streptozotocin. BMC Nephrol 2020;21:174.

72. Liu Zh, Zhang W. Protective effect of berberine on renal fibrosis caused by diabetic nephropathy. Mol Med Rep 2017;16:1055-62.

73. Li Z, Hong Z, Peng Z, Zhao Y, Shao R. Acetylshikonin from Zicao ameliorates renal dysfunction and fibrosis in diabetic mice by inhibiting TGF-β1/Smad pathway. Hum Cell 2018;31:199-209.

74. Loeffler I, Wolf G. Epithelial-to-Mesenchymal Transition in Diabetic Nephropathy: Fact or Fiction? Cell 2015;4:631-52.

75. Singh M, Yelle N, Venugopal C, Singh SK. EMT: Mechanisms and therapeutic implications. Pharmacol Ther 2018;182:80-94.

76. Hsu YC, Chang PJ, Tung CW, Shih YH, Ni WC, Li YC, et al. De-Glycyrrhizinated Licorice Extract Attenuates High Glucose-Stimulated Renal Tubular Epithelial-Mesenchymal Transition via Suppressing the Notch2 Signaling Pathway. Cells 2020;9:125.

77. Ruan Y, Yuan PP, Wei YX, Zhang Q, Gao LY, Li PY, et al. Phenolic Compounds from Mori Cortex Ameliorate Sodium Oleate-Induced Epithelial-Mesenchymal Transition and Fibrosis in NRK-52E Cells through CD36. Molecules 2021;26:6133.

78. Lv ZM, Wang Q, Wan Q, Lin JG, Hu HY, Liu YX, et al. The role of the p38 MAPK signaling pathway in high glucose-induced epithelial-mesenchymal transition of cultured human renal tubular epithelial cells. PLoS One 2011;6:e22806.

79. Dong Z, Sun Y, Wei G, Li S, Zhao Z. A Nucleoside/Nucleobase-Rich Extract from Cordyceps Sinensis Inhibits the Epithelial-Mesenchymal Transition and Protects against Renal Fibrosis in Diabetic Nephropathy. Molecules 2019;24:4119.

80. L. Wu Z, Xue S, Zheng B, Ye R, Xu G, Zhang S, et al. Kidney-targeted baicalin-lysozyme conjugate ameliorates renal fibrosis in rats with diabetic nephropathy induced by streptozotocin. BMC Nephrol 2020;21:174.

81. Tao M, Zheng D, Liang X, Wu D, Hu K, Jin J, et al. Tripterygium glycoside suppresses epithelial-mesenchymal transition of diabetic kidney disease podocytes by targeting autophagy through vitamin beta-catenin transcriptional activity under high glucose conditions. Int J Biochem Cell Biol 2013;45:255-64.

82. Sun LN, Chen ZX, Liu XC, Liu HY, Gao BJ, Liu G. Curcumin ameliorates epithelial-mesenchymal transition of podocytes in vivo and in vitro via regulating caveolin-1. Biomed Pharmacother 2014;68:1079-88.

83. Turkmen K. Inflammation, oxidative stress, apoptosis, and autophagy in diabetes mellitus and diabetic kidney disease: the Four Horsemen of the Apocalypse. Int Urol Nephrol 2017;49:837-44. I.

84. Xiao Y, Jiang X, Peng C, Zhang Y, Xiao Y, Liang D, et al. BMP-7/Smads-induced inhibitor of differentiation 2 (Id2) upregulation and Id2/Twist interaction was involved in attenuating diabetic renal tubulointerstitial fibrosis. Int J Biochem Cell Biol 2019;116:105613.

85. Setoyama T, Nakada T, Yoshida M, Kurata K, Nakamura S, et al. Expression of EMT markers in diabetic nephropathy and association with loss of epithelial phenotype and EMT. Diabet Med 2017;34:594-602.

86. Wu Z, Xue S, Zheng B, Ye R, Xu G, Zhang S, et al. Expression and significance of e-kid and epithelial-mesenchymal transition (EMT) molecules in thymic epithelial tumors (TETs). J Thorac Dis 2019;11:4602-12.
87. Xiao Y, Peng C, Xiao Y, Liang D, Yuan Z, Li Z, et al. Oxymatrine Inhibits Twist-Mediated Renal Tubulointerstitial Fibrosis by Upregulating Id2 Expression. Front Physiol 2020;11:599.
88. Zhang Y, Sun X, Icli B, Feinberg MW. Emerging roles for microRNAs in diabetic microvascular disease: novel targets for therapy. Endocr Rev 2017;38:145-68.
89. Chandrasekaran K, Karolina DS, Sepramaniam S, Armugam A, Wintour EM, Bertram JF, et al. Role of microRNAs in kidney homeostasis and disease. Kidney Int 2012;81:617-27.
90. Trionfini P, Benigni A, Remuzzi G. MicroRNAs in kidney physiology and disease. Nat Rev Nephrol 2015;11:23-33.
91. Zou XZ, Liu T, Gong ZC, Hu CP, Zhang Z. MicroRNAs-mediated epithelial-mesenchymal transition infibrotic diseases. Eur J Pharmacol 2017;796:190-206.
92. Assmann TS, Recamonde-Mendoza M, de Souza BM, Bauer AC, Crispim D. MicroRNAs and diabetic kidney disease: systematic review and bioinformatic analysis. Mol Cell Endocrinol 2018;477:90-102.
93. Dewanjee S, Bhattacharjee N. MicroRNA: A new generation therapeutic target in diabetic nephropathy. Biochem Pharmacol 2018;155:32-47.
94. Li YK, Ma DX, Wang ZM, Hu XF, Li SL, Tian HZ, et al. The glucagon-like peptide-1 (GLP-1) analog liraglutide attenuates renal fibrosis. Pharmacol Res 2018;131:102-11.
95. Jia Y, Zheng Z, Guan M, Zhang Q, Li Y, Wang L, et al. Exendin-4 ameliorates high glucose-induced fibrosis by inhibiting the secretion of miR-192 from injured renal tubular epithelial cells. Exp Mol Med 2018;50:1-13.
96. Jia Z, Wang K, Zhang Y, Duan Y, Xiao K, Liu S, et al. Icariin Ameliorates Diabetic Renal Tubulointerstitial Fibrosis by Restoring Autophagy via Regulation of the miR-192-5p/GLP-1R Pathway. Front Pharmacol 2021;12:720387.
97. Wang JY, Gao YB, Zhang N, Zou DW, Xu LP, Zhu ZY, et al. Tongxinluo ameliorates renal structure and function by regulating miR-21-induced epithelial-to-mesenchymal transition in diabetic nephropathy. Am J Physiol Renal Physiol 2014;306:F486-95.
98. Wang X, Gao Y, Tian N, Zou D, Shi Y, Zhang N. Astragaloside IV improves renal function and fibrosis via inhibition of miR-21-induced podocyte dedifferentiation and mesangial cell activation in diabetic mice. Drug Des Devel Ther 2018;12:2431-42.
99. Tian C, Wang Y, Chang H, Li J, La X. Spleen-Kidney Supplementing Formula Alleviates Renal Fibrosis in Diabetic Rats via TGF-β1-miR-21-PTEN Signaling Pathway. Evid Based Complement Alternat Med 2018;2018:3824357.
100. Klimczak D, Kuch M, Pilecki T, Zochowska D, Wirkowska A, Pączek L, et al. Plasma microRNA-155-5p is increased among patients with chronic kidney disease and nocturnal hypertension. J Am Soc Hypertens 2017;11:831-41.
101. Guo L, Tan K, Luo Q, Bai X. Dihydromyricetin promotes autophagy and attenuates renal interstitial fibrosis by regulating miR-155-5p/PTEN signaling in diabetic nephropathy. Bosn J Basic Med Sci 2020;20:372-80.
102. Xu Y, Zhang J, Fan L, He X. miR-423-5p suppresses high-glucose-induced podocyte injury by targeting Nox4. Biochem Biophys Res Commun 2018;505:339-45.
103. Hou Y, Zhang Y, Lin S, Yu Y, Yang L, Li L, et al. Protective mechanism of apigenin in diabetic nephropathy is related to its regulation of miR-423-5P-USF2 axis. Am J Transl Res 2021;13:2006-20.