Review Article

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,

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Submitted: 28-Mar-2022 **Revised:** 19-May-2022
Accepted: 30-Jul-2022 **Published:** 27-Sep-2022

Access this article online

Quick Response Code:

Website: www.journal-imna.com

DOI: 10.4103/2773-0387.353727

How to cite this article: Jiang T, Bao Y, Su H, Zheng R, Cao L. Mechanisms of Chinese Herbal Medicines for Diabetic Nephropathy Fibrosis Treatment. J Integr Nephrol Androl 2022;9:11.

as well as the reduction of urinary albumin.[3] 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.[4] CHMs have several advantages over standard medical treatments for the prevention of DN due to their lower toxicity or fewer side effects.[5-7] In recent years, many investigations have revealed that attempts to treat DN with CHMs have achieved some efficacy.[8] 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.[9] 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.[10] 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.[11] 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.[12-14] These proinflammatory cytokines are key regulators of fibrosis and are significantly related to proteinuria and glomerular basement membrane thickening.[15] Various Chinese medicines, including formula preparations and single herbs or their active ingredients, can ameliorate renal fibrosis in DN by inhibiting inflammation [Figure 1].

Arabinoglucan (AG), isolated from Angelica sinensis, exhibits anti-inflammatory activities.[16] 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.[17] 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.[18] Jowiseungki decoction, which is composed of three herbs (rhubarb, mirabilitum, and licorice), also prevents inflammation-induced renal fibrosis via the downregulation of NF-κB.[19] 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.[20] Furthermore, the G-protein-coupled bile acid receptor Gpbar1 (TGR5) inhibits the NF-κB signaling pathway. Gentiopicroside, 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.[21]

Bupleurum polysaccharides (BPs), which are derived from the root of Bupleurum smithii var. parvifolium, exert anti-inflammatory and antioxidant effects.[22-23] The therapeutic effectiveness of BPs in suppressing inflammatory reactions might be linked to modulation of the TLR4 signaling pathway.[24] 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.[25] 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.[26-27] 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.[28] In addition, high-mobility group box 1 (HMGB1), which can be passively released by cells damaged by diabetes, is an endogenous ligand of TLR4.[29-30] The release of HMGB1 can be induced by hyperglycemia, which causes tubulointerstitial inflammation during the progression of DN.[31] 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.[30] These proinflammatory responses result in the accumulation of fibronectin in the

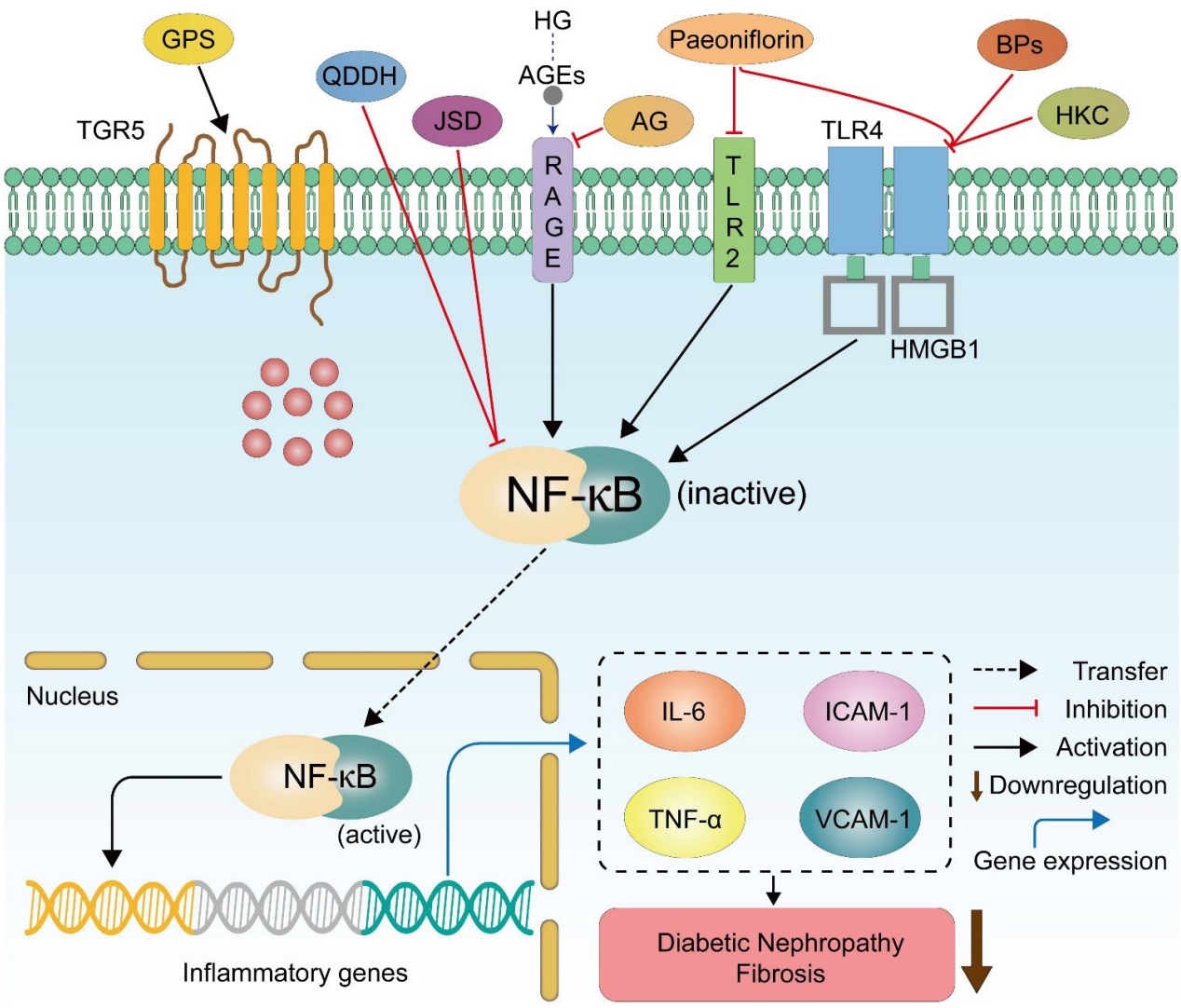

Figure 1: Chinese medicines can protect against diabetic nephropathy fibrosis via inhibiting inflammation by blocking NF-κB, TLR-2/4, and HMGB1/TLR4 signaling pathways and activating TGR5. In hyperglycemia-affected tissues, excessive AGE-RAGE interactions will stimulate a variety of proinflammatory cellular responses. In diabetic kidneys, an increase of NF-κB activation leads to the overexpression of inflammatory cytokines, including TNF-α, IL-6, ICAM-1, and VCAM-1. AG, Arabinoglucan; QDDH, Qi-dan-di-huang; JSD, Jowiseungki decoction; BPs, Bupleurum polysaccharides; HKC, Huangkui capsule; GPS, gentiopicroside; TGR5, the G-protein-coupled bile acid receptor Gpbar1; HG, high glucose; AGEs, advanced glycation end products; RAGE, receptor for AGE; TLRs, Toll-like receptors; HMGB1, High-mobility group box 1; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; IL-6, interleukin-6; TNF-α, tumor necrosis factor-α; ICAM-1, intercellular adhesion molecule-1; VCAM-1, vascular cell adhesion molecule-1.

fibrosis process.[32] Liu *et al*.[33] 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,[34] and it is well acknowledged that EMT is a significant process in the early stage of renal interstitial fibrosis (RIF).[35] 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.[36] Following the activation of inducible nitric oxide synthase (iNOS), a substantial amount of nitric oxide, a hallmark of macrophage activation, is produced.[37] Liao *et al*.[38]

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.[39] 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.[40-41] In patients with diabetes, hyperglycemia upregulates the most important resource of ROS, nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (Nox) in intrinsic renal cells.[42] 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.[43] Moreover, macromolecule oxidative products such as malondialdehyde (MDA), 8-hydroxy-2-deoxyguanosine, and oxidative carbonyl proteins are elevated in the kidney.[44] 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.[45] Simultaneously, the activity of antioxidant enzymes such as superoxide dismutase (SOD) is usually decreased in the diabetic state.[44]

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.[46] 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.[47] 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.[48] Tetrandrine (Tet), a bisbenzylisoquinoline alkaloid, is isolated from the roots of Stephania tetrandra.[49] Su *et al*.[50] demonstrated that Tet could significantly restrain renal damage by upregulating the expression of p-Nrf2 and HO-1. Ho *et al*.[51] 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 H_2O_2-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.[52] 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.[53] 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 TGFβ1, 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.[54] 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.[55] In both experimental animal models and human kidney disorders, TGF-β1 causes fibrinogenesis by stimulating the downstream Smad signaling pathway.[56] 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,[57] to promote the expression of genes associated with renal fibrosis.[58] It has been reported that TGF-β1 promotes Smad3 to induce fibrosis, whereas the overexpression of Smad7 inhibits fibrosis in the kidney.[59-60]

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.[61] Chaihuang-Yishen granule (also called Qilong-Lishui granule) is manufactured based on the TCM theory for the treatment of DKD and blocks TGF-β/Smad3-mediated renal fibrosis to attenuate DN.[62] Hu *et al*.[63] demonstrated that treatment with rhein, an extract of the Chinese herb rhubarb, significantly reduces the level of TGF-β1 in animals with DN. Taxus chinensis, 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.[64] Peroxisome proliferator-activated receptor (PPAR) activation

mitigates aldosterone-induced mitochondrial dysfunction in podocytes.[65] Huangqi Decoction, composed of seven herbs (Astragalus, Poria, Trichosanthes, Ophiopogon, Schisandra, Licorice, and Rehmannia), ameliorates DN by regulating TGF-β1/MAPK/PPAR-γ signaling.[66] Artemisinin (ATZ) is obtained mostly from the Artemisia annua (Asteraceae).[67] 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.[68] Baicalin, a main bioactive component of Scutellaria baicalensis, has traditionally been widely used to treat DN and can attenuate ECM via the TGF-β/Smad3 pathway.[69] 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.[70] Li *et al*.[71] showed that acetylshikonin, 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.[72] 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.[73] 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.[74] Ruan *et al*.[75] reported that phenolic compounds from Mori Cortex inhibit EMT caused by sodium oleate-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.[76] 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.[77] β-catenin is a transcriptional coactivator in the Wnt/β-catenin signaling pathway, which hastens EMT development in podocytes.[78] Sun *et al*.[79] 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.[80] 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-renal fibrosis effects that can protect against EMT by enhancing autophagy.[81] Astragaloside IV (AS-IV), one of the bioactive saponin extracts of Astragalus root, may also exert effects on podocyte EMT by activating autophagy.[82] During the EMT process, the expression of some antifibrotic regulators, such as inhibitor of differentiation 2 (Id2), is decreased.[83] 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*.[87] 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

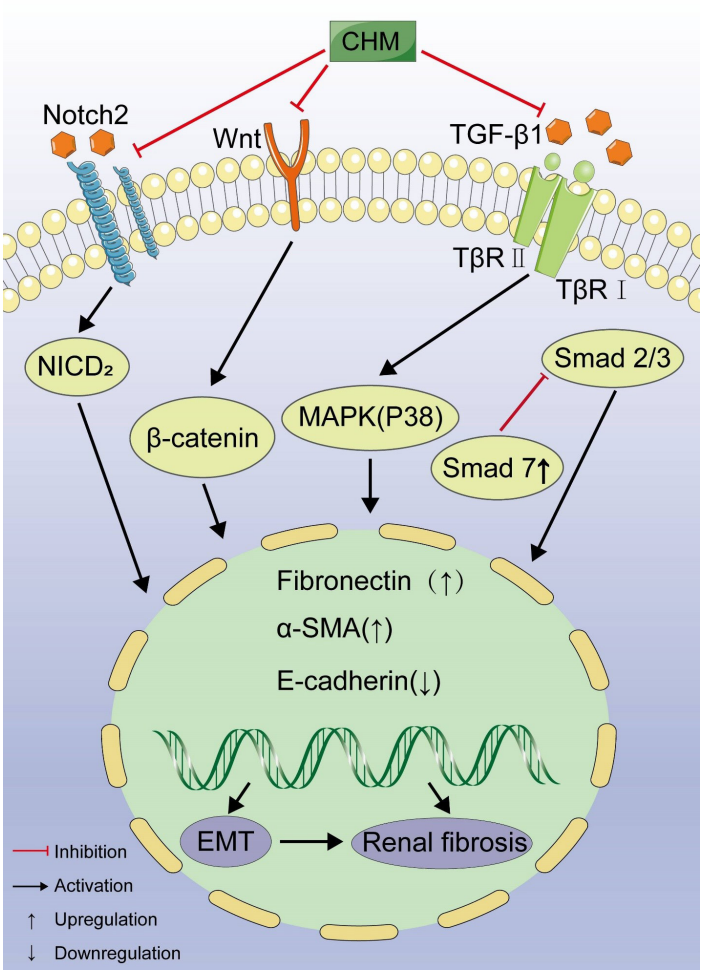

Figure 2: CHMs attenuate renal fibrosis in diabetic nephropathy by regulating TGF and inhibiting EMT through suppressing Notch2, Wnt/β-catenin, p38 MAPK signaling pathway. It is reported that some CHMs contribute to reductions in TGF-β1 expression and Smad2/3 phosphorylation and increases in Smad7 expression. 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 Supplementing 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 vivo* 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
Arabinoglucan	*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*.[16]	2018
Gentiopicroside	*Gentiana manshurica Kitagawa*	TGR5, NF-κB	Anti-inflammation	Xiao *et al*.[21]	2020
Huangkui capsule	*Abelmoschus manihot*	NLRP3, TLR4/NF-κB signaling	Alleviation of renal tubular EMT and inflammation reactions	Han *et al*.[34]	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*.[38] Wang *et al*.[82, 98]	2017 2019 2018
Lycium chinense leaf extract	*Solanaceae*	GSH, SOD, CAT, MDA, TNF-α, IL-6, IL-1β	Antioxidative stress and inflammation	Olatunji *et al*.[46]	2018
Tetrandrine	*Stephania tetrandra*	p-Nrf2, HO-1	Antioxidative stress	Su *et al*.[49]	2020
Curcumin	*Rhizoma Curcuma longae*	Superoxide, Wnt/β-catenin signaling pathway	Preventing ECM accumulation and oxidative stress, attenuating EMT	Ho *et al*.[51] Sun *et al*.[79]	2016 2015
Nepeta angustifolia	*Schizonepeta tenuifolia Briq.*	SOD, ROS, MDA	Reducing cell damage and oxidative stress	Huang *et al*.[52]	2020
Rhein	*Rhubarb*	TGF-β1	Regulation of TGFs	Hu *et al*.[63]	2019
Taxus chinensis	*Taxaceae*	TGF-β1, α-SMA, Smad2, Smad3	Regulation of TGFs	Hong-Bo *et al*.[64]	2018
Artemisinin	*Artemisia annua*	TGF-β1, Nrf2	Antioxidative stress and regulation of TGFs	Zhang *et al*.[67]	2020
Baicalin	*S. baicalensis*	TGF-β/Smad3 signaling pathway	Attenuation of ECM and regulation of TGFs	Zheng *et al*.[69]	2020
Acetylshikonin	*Arnebia euchroma*	TGF-β1, Smad2/3, Smad7, PAI-1, Collagen III and IV	Regulation of TGFs and reduction of fibrosis proteins	Li *et al*.[71]	2018
Licorice extract	*Glycyrrhiza*	Notch2 signaling pathway, NRK-52E cells	Attenuation of EMT	Hsu *et al*.[74]	2020
Mori Cortex	*Morus alba L*	NRK-52E cells, CD36	Attenuation of EMT	Ruan *et al*.[75]	2021
Cordyceps	*Cordyceps sinensis*	p38 MAPK signaling pathway	Attenuation of EMT	Dong *et al*.[77]	2019
Tripterygium glycoside	*Tripterygium wilfordii*	Autophagy	Attenuation of EMT	Tao *et al*.[81]	2021
Oxymatrine	*Sophora flavescens*	Id2, Twist	Attenuation of EMT	Xiao *et al*.[87]	2020
Icariin	*Herba epimedii*	MiR-192, GLP-1R	Regulation of miRNAs	Jia *et al*.[96]	2021
Dihydromyricetin	*Ampelopsis Michx*	MiR-155-5p, NRK-52E cells	Regulation of miRNAs	Guo *et al*.[101]	2019
Apigenin	*Celery*	MiR-423-5p	Regulation of miRNAs	Hou *et al*.[103]	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.

Acknowledgement

The authors are grateful to the dedicated and committed participants in this study.

Financial support and sponsorship

The study was funded by the Fourth Session Clinical Talents (Western) Program of the National Traditional Chinese Medicines, the State Administration of Traditional Chinese Medicine, Talent and Education of Traditional Chinese Medicines [2019] No. 13. The study was also supported by Jiangsu province Health and Family Planning Commission (BJ2017029).

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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*.[19]	2020
Qi-dan-di-huang	Astragalus, Salvia miltiorrhiza, Radix Rehmanniae, Chinese yam, licorice	NF-κB pathway	Anti-inflammation	Ma *et al*.[20]	2019
Liuwei Dihuang pill	Rehmannia glutinosa, Cornus, Yam, Cortex moutan, Rhizoma alismatis, Tuckahoe	SOD, NOS, MDA	Antioxidative stress and protection of the function of mesangial cells	Xu *et al*.[53]	2017
Chaihuang-Yishen granule	Astragalus, Pyrrosia, Angelica sinensis, Bupleurum, Rhizoma Dioscoreae Nipponicae, Polyporus, Leeches	TGF-β/Smad3 signaling pathway	Regulation of TGFs	Zhao *et al*.[62]	2014
Huangqi Decoction	Astragalus, Poria, Trichosanthes, Ophiopogon, Schisandra, Licorice, Rehmannia	TGF-β1, MAPK, PPAR	Regulation of TGFs	Han *et al*.[66]	2017
Spleen-Kidney Supplementing Formula	Radix Astragali, Fructus Corni, Rhizoma Coptidis, Cortex Mori, Radix Puerariae Lobatae, Herba Eupatorii	MiR-21	Regulation of miRNAs	Tian *et al*.[99]	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.

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