



Regulation of Chinese Herbal Medicines in Inflammation of Diabetic Nephropathy*

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Abstract With increasing incidences of diabetes, diabetic nephropathy (DN) becomes the leading cause of chronic kidney disease and end-stage (ESRD) renal disease worldwide. However, the current pharmacological treatments for glycemic control and inhibitors of the renin-angiotensin system cannot effectively prevent the progression of DN. Recent studies show that the chronic low-grade inflammation and activation of the immune system have emerged as a paramount role in the development and progression of DN. Understanding the inflammatory cascade and mechanisms in the progression of DN will enable identification of new potential targets and facilitate the design of innovation anti-inflammatory therapeutic strategies. Growing evidence has demonstrated that the treatment of Chinese herbal medicines for DN improves hyperglycemia and proteinuria interrupting progression to ESRD. Chinese herbal medicines including herbal formulas, single herbal medicines, extracts of herbs, and compounds from herb, have been proved to regulate inflammation in DN animal and cell line models. In this review, we focus on inflammatory molecules and pathways in relation to renal injury of DN, and discuss potential traditional Chinese medicine (TCM) strategies to treat DN *via* targeting inflammatory factors.

Key words diabetic nephropathy, inflammation, Chinese herbal medicines

DOI: 10.16476/j.pibb.2020.0188

Diabetic nephropathy (DN) is a serious complication of diabetes mellitus (DM) affecting 30% individuals with diabetes throughout the world. Increasing incidences of diabetes make DN become the most significant leading cause of end-stage renal disease (ESRD)^[1]. Thus the improvement of health outcomes for DN needs to refocus on the strategies for controlling the progression of DN to the ESRD.

DN is characterized by glomerular hypertrophy, thickness of basement membrane, podocyte effacement, diffuse mesangial matrix expansion and capillary wall thickening, and finally progresses to glomerulosclerosis and tubulointerstitial fibrosis^[2]. The traditional understanding of the pathogenesis of DN recognizes the involvement of metabolic abnormalities, hemodynamic changes, renin-angiotensin system (RAS) activation, and oxidative stress. However, a variety of recent researches show that the inflammation regulators involved in DN, such as increasing levels of inflammatory mediators and infiltration of immune cells in renal tissue of DN

patients and animal models, or upregulating adhesion molecules and chemokines in diabetic kidneys^[3]. The inhibition of inflammatory cell recruitment has been investigated to protect the renal tissue in DN animal models^[4-5]. As a result, there is growing support for the notion that chronic low-grade inflammation and activation of the immune system play a crucial role in the pathogenesis of DM and progression of DN. Hemodynamic abnormalities and metabolic disruptions, which are deviations from normal homeostasis associated with DM, activate kidney cells to produce proinflammatory responses and release

* This work was supported by grants from the International Cooperation Base for Prevention and Treatment of Chronic Diseases with Traditional Chinese Medicine (GZYYGJ2019034), International Research Center for the Prevention and Treatment of Diabetes with Traditional Chinese Medicine (2015B01022), and Beijing International Science and Technology Cooperation Base.

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Received: June 2 2020 Accepted: June 10, 2020

chemokines and adhesion molecules leading to facilitate innate immune response in the kidney as shown in Figure 1. It will enable identification of new potential targets and facilitate the design of innovation anti-inflammatory therapeutic strategies that the inflammatory mechanisms are well understood in the

progression of DN. In this review, we focus on inflammatory molecules and pathways in relation to renal injury of DN, and discuss potential traditional Chinese medicine (TCM) strategies to treat DN *via* targeting inflammatory factors.

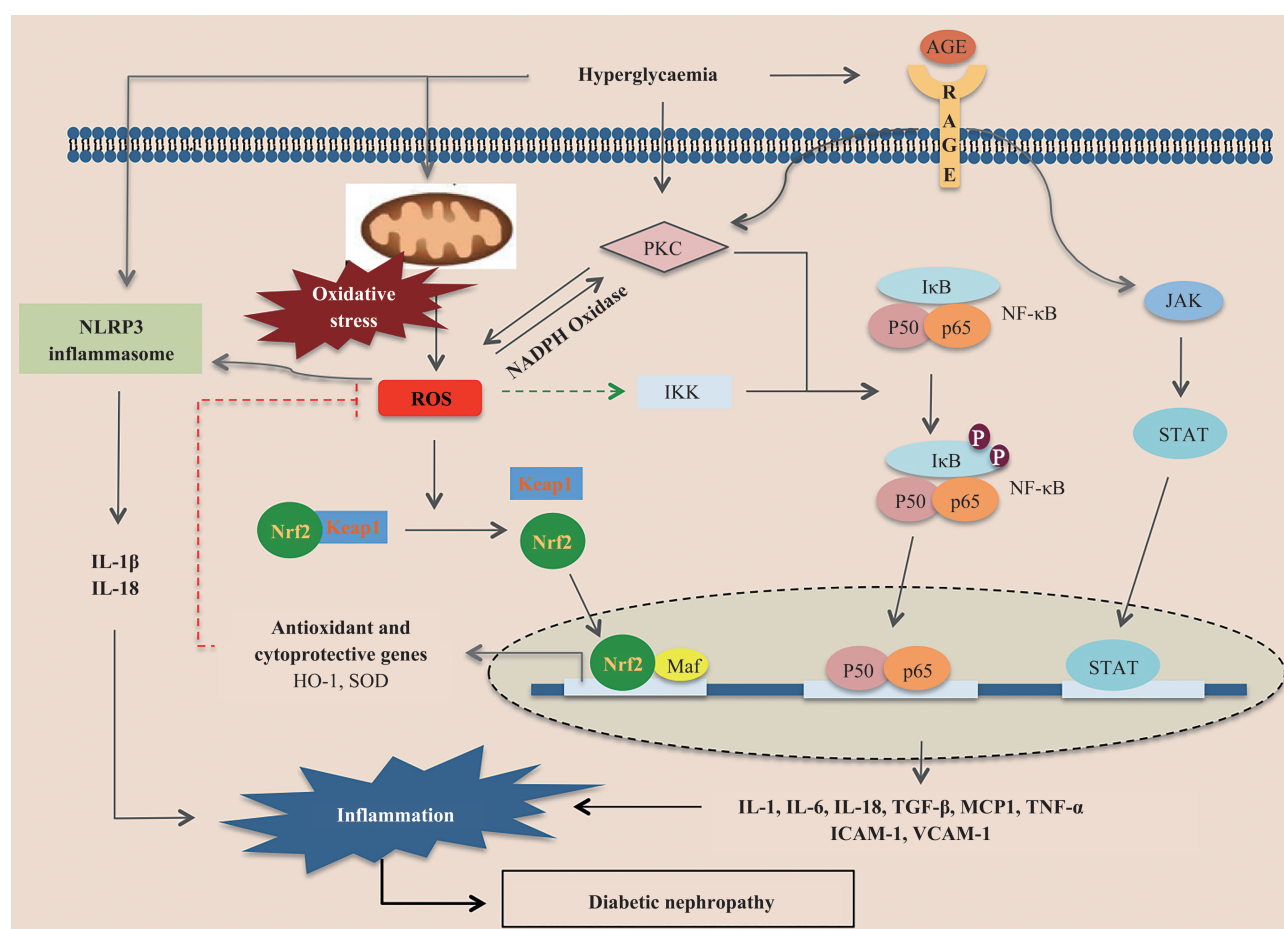


Fig. 1 The overview of participation inflammatory mechanisms in the pathogenesis of diabetic nephropathy

1 Inflammation and DN

1.1 Inflammatory signal pathways

The accumulated evidences indicated that several signaling cascades are the key factors in the development and progression of renal inflammation. These pathways response and transduce the signals of upstream mediators including oxidative stress, advanced glycation end products (AGEs), and angiotensin II, resulting in decreased renal function.

NF-κB, a transcription factor that controls different genes expression involved in multiple processes including the immune response, apoptosis,

cell differentiation, tumorigenesis and inflammation, is activated by many stimuli related to DN. NF-κB regulates inflammatory cytokines, chemokines, and adhesion molecules, which contribute to renal injury partly, through oxidative stress, AGEs, and protein kinase C (PKC) in hyperglycemia^[6]. NF-κB plays a central role in inflammation with regulating factors, molecules, microRNA and interactive pathways, and mediating transcription biological messages resulting in pathogenesis of DN. The activation of NF-κB has been observed in renal cells and kidneys of DN animal models^[3]. Furthermore, the suppression of NF-κB activation has been demonstrated to ameliorate renal injury in DN^[7].

Janus kinase/ signal transducer and activator of transcription (JAK/STAT) pathway is a major pathway responding and transducing inflammatory signal, which transmits extracellular ligand signal such as cytokines, chemokines, and growth factors directly to the cell nucleus. It has been demonstrated that the JAK/STAT pathway in the glomeruli and tubulointerstitial cells is activated in animal models and clinical studies of DN^[8-9].

Nuclear factor erythroid 2-related factor 2 (Nrf2) is a transcription factor regulating the cellular antioxidant response to counteract renal damage in diabetes^[10]. Nrf2 directly mediates the transcription of pro-inflammatory cytokines including IL1 and IL6 to inhibit renal inflammation^[3]. Nrf2 dysfunction potently activates NF- κ B and participates in the renal inflammation. Nrf2^(-/-) mice produce greater amounts of ROS and intensify inflammation leading to renal injury compared with wild mice^[11].

The Rho-associated coiled-coil containing protein kinase (Rho-kinase) is involved in the regulation of cell function such as cell proliferation, contraction, migration, and transcriptional regulation by acting on the cytoskeleton^[7]. Rho-kinase regulates the production of MCP1 and monocyte chemotaxis to glomerular cells and NF- κ B activation against renal inflammation^[3]. The inhibition of Rho-kinase improves albuminuria, glomerular matrix expansion^[12-13], and infiltration of macrophages^[14] in DN animal models.

1.2 Immunity and inflammatory mediators

1.2.1 Chemokines

Chemokines involved in inflammatory response have been reported to play an important role in the pathogenesis of DN. C-C motif chemokine 2 (CCL2), known as monocyte chemoattractant protein 1 (MCP-1), mediates the migration of monocytes and macrophages into kidney tissue, while CX3-C motif chemokine 1 (CX3CL1) and C-C motif chemokine 5 (CCL5) are chemoattractants for monocytes, macrophages, and T cells^[1]. The induction of MCP-1 by inflammatory cytokines in renal cells constitutes the starting point for glomerular and tubular inflammation. In type 2 diabetic patients, the increased level of urinary MCP-1 is strongly related to urinary albumin excretion and the decline of renal function^[15]. However, the deficient of MCP-1 in type

1 and type 2 diabetic mice models could protect from renal injury^[16-17]. These findings suggest that MCP-1 level should be proposed as a novel biomarker of tubular injury for predicting progression in DN patients.

1.2.2 Adhesion molecules

Adhesion molecules including immunoglobulin superfamily and selectins are located on cell surfaces involved in binding with other cells or with the extracellular matrix. Growing studies have shown significant increases in intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion protein 1 (VCAM-1) play an important role in the initiation of renal inflammation^[11]. Both molecules have been abundantly found in renal biopsies of patients with DN and contributed to DN progression^[18]. It has been indicated that the deletion of the ICAM1 gene ameliorates renal inflammation in diabetic mice models^[19].

1.2.3 Inflammatory cytokines

Cytokines, polypeptides involved in autocrine, paracrine and juxtacrine, have pleiotropy, diversity, and synergy to regulate inflammatory process and immune system. Interleukin 1(IL-1), IL-6, IL-18, and tumor necrosis factor (TNF) are considered the crucial inflammatory cytokines in DN^[20].

IL-1 is indicated to increase the expression of chemotactic factors and adhesion molecules including ICAM-1 and VCAM-1, enhance vascular endothelial permeability, and stimulate the proliferation of mesangial cells and matrix synthesis, and induce TGF- β 1 production in diabetic kidney^[21-23]. Furthermore, IL-1 raises the production of hyaluronan by epithelial cells of renal proximal tubule^[24], associated with the development of hypercellularity in diabetic rats^[25].

Serum IL-6 levels are significantly higher in DN patients compared to diabetic patients without renal injury^[25]. In addition, the kidneys of patients with DN display increased expression levels of IL-6 in infiltrating cells from mesangium, interstitium, and tubules^[26]. Moreover, IL-6 is positively related to diverse abnormalities of diabetic kidney and progression of renal damage including changes in the permeability of glomerular endothelium, the mesangium expansion, increased fibronectin levels, and thickness of the glomerular basement membrane^[27-28].

IL-18 is a potent inflammatory cytokine to induce interferon- γ (IFN- γ), stimulate the production of other inflammatory cytokines (IL-1, IL-6 and TNF- α), increase the expression of ICAM-1, and contribute to apoptosis endothelial cells^[21,29]. Serum and urinary levels of the cytokine IL18 are significantly increased in DN patients correlated with urinary albumin levels^[29-30]. Moreover, the expression of IL-18 in renal tubular cells also rises in DN patients^[31].

TNF, mainly produced by infiltrating cells, is a key inflammatory cytokine in the progression of renal disorders. It has been found that serum and urinary levels of TNF in patients with DN increase according to the progression of DN^[32]. The expression levels of TNF protein from renal glomeruli and tubules are also enhanced in diabetic animal models^[33]. Increased TNF expression levels have been associated with hypertrophy and hyperfiltration that are prominent signs in DN. In addition, TNF- α alters glomerular hemodynamics and increases vascular endothelium permeability to decrease glomerular filtration rate (GFR), and also promote production of ROS in renal structures^[34].

1.2.4 NLRP3 inflammasome

The NLRP3 inflammasome can convert the pro-inflammatory cytokines IL-1 β and IL-18 to their active forms in response to host or pathogen derived, as well as mediate a form of inflammatory cell death, which has been implicated in the pathogenesis of diabetic nephropathy^[35-36].

2 Chinese herbal medicine as a therapeutic approach to inflammation in DN

Increasing clinical and experimental studies have demonstrated that traditional Chinese medicine (TCM) approaches to treatment of DN improve hyperglycemia and proteinuria interrupting progression to ESRD^[37]. At the present time, the efficiency and underlying mechanisms of Chinese herbal medicines have been shown clearly in diabetes and its complications by phytochemistry and molecular biology. As compelling evidence supporting an important role of immunity and inflammation in the pathogenesis of DN, we will address the current status of Chinese herbal medicines including single herbal medicines, extracts of herbs, and herbal formulas as therapeutic targets for DN regulating inflammatory mediators.

2.1 Effect on inflammatory signal pathways

Chinese herbal medicines are applied as formulas, extracts of herbs and compounds mediating several inflammatory signaling cascades in DN. These medicines mainly involve the regulation of NF- κ B, but also in a lower extent, Nrf2, RhoA/ROCK, and JAK2/STAT pathways. That mentioned in the review are shown in Table 1.

2.1.1 Effect on NF- κ B pathway

2.1.1.1 Formulas. Formula, the TCM prescriptions composed of herbs, has been widely used for various diseases in the China throughout thousands of years. Recent studies show that formulas could ameliorate renal inflammation to protect kidney in DN. Inhibition of NF- κ B pathway plays an important role in these formula mediating reduction in the inflammatory process. Furthermore, downstream targets of NF- κ B including inflammatory cytokines and adhesion molecules (ICAM-1, MCP-1, TNF- α , IL-1 β , and IL-6) are also regulated by the formula.

Jiangtang decoction, a Chinese patented drug (Patent Number: 20141002188.3), contains *Euphorbia humifusa* Willd, *S. miltiorrhiza* Bunge, *A. mongholicus* Bunge, *A. asphodeloides* Bunge, and *C. chinensis* Franch. Jiangtang decoction alleviates renal inflammation indexes ICAM-1, TNF- α , and IL-6 and inhibits NF- κ B signaling pathway to attenuate DN in KK-Ay mice^[38]. Also, *Tang shen* formula including *Radix puerariae*, *astragalus*, *Ligustrum lucidum*, *Lucid ganoderma*, *Salvia miltiorrhiza* and *Rheum rhabarbarum* improves inflammation in renal tissue through SIRT1/NF- κ B pathway, resulting in inhibition of inflammatory factors MIF and MCP-1 in high-fat diet/STZ-induced diabetic rats^[39]. Additional, another *Tang shen* formula consisted of *astragalus* root, burning bush twig, *rehmannia* root, bitter orange, cornus fruit, rhubarb root and rhizome, *notoginseng* root, attenuates DN associated with an inactivation of NF- κ B signaling, thereby blocking the upregulation of pro-inflammatory cytokines (IL-1 β , TNF- α), chemokine (MCP-1), and macrophage infiltration in the high-fat diet/STZ-induced diabetic rats^[40]. Besides, *Xiexin* decoction including *Rhizoma Coptidis* alkaloids, *Radixet Rhizoma Rhei* polysaccharides, and *Radix Scutellaria* flavones, alleviates renal injury of DN through reducing MCP-1, TNF- α , and IL-6 and downregulation of NF- κ B pathway in high-fat diet/STZ-induced rats and high glucose-induced rat

mesangial cells^[41]. Moreover, combination of active components of *Xiexin* Decoction ameliorates renal injury *via* inhibiting inflammation mediators such as TNF- α and IL-1 β , ICAM-1, and MCP-1 and through NF- κ B pathway in db/db mice and high glucose cultured mesangial cells^[42].

2.1.1.2 Extracts of herbs. The extracts of Chinese herbs display renal protection from inflammation *via* targeting the specific pathways involved in DN. Calycosin, the extract from *Radix astragali*, significantly inhibits AGEs-driven inflammation *via* the NF- κ B signaling pathway and inflammatory cytokine TNF- α and IL-1 β in db/db mice kidney and mouse tubular epithelial cells^[43]. An aqueous extract of *Portulaca oleracea*^[44], *Prunella vulgaris*^[45], *Andrographolide*^[46], *Morroneiside* (isolated from *Corni Fructus*)^[47] inhibit the NF- κ B signaling pathway and suppress inflammatory mediators in HG-induced human mesangial cell and diabetic animal models. Meanwhile, the herb injections also have the effect on inflammation. Danshen injection, extracted from anti-inflammatory herb *Salvia miltiorrhiza*^[48], could suppress oxidative stress and alleviate renal inflammation through suppressing I κ B/NF- κ B signaling pathway and reducing the level of a number of pro-inflammatory factors such as TNF- α , IL-1 β and IL-6 in STZ-induced diabetic rats^[49].

2.1.1.3 Compounds. There is an increasing interest of compounds from single Chinese herbal medicines for the treatment of DN, since they are more appropriate to clarify the precise action mechanism. Growing evidence demonstrates that compounds regulate inflammatory pathways to protect kidney from damage in diabetes. Moreover, some compounds mitigate renal inflammation of DN not only through signaling cascades, but also pro-inflammatory cytokines, chemokines, and the anti-inflammatory factor.

Lycium barbarum polysaccharides ameliorate renal injury and postpone the appearance and development of DN relating to restraining the expression of NF- κ B and AngII, in turn the reduction the expression of MCP-1 mRNA and ICAM-1 mRNA in alloxan-induced diabetic rabbits^[50]. *Mangiferin* prevents the renal glomerulus fibrosis through suppression of inflammation likely *via* inactivation of NF- κ B and reduction of the levels of IL-1 β in STZ-induced diabetic rats^[51]. *Geniposide* also improves diabetes-induced GBM changes *via* suppression of

NF- κ B mediated expression of ICAM-1, TNF- α , IL-1, and IL-6 and enhancement of monocytes and T lymphocytes infiltration in streptozotocin-induced diabetic rats^[52]. *Ruscogenin*^[53] isolated from *Ruscus aculeatus* and *Astragaloside IV*^[54] purified from *Astragalus membranaceus*, both inhibit NF- κ B-mediated inflammatory pathway and downregulating ICAM-1 and MCP-1 in streptozotocin-induced diabetic rat. Besides in diabetic animal models, *Coreopsis tinctoria* Nutt^[55] and *Quercetin*^[56] mediates NF- κ B signaling pathway following downregulation of MCP-1 to inhibit inflammation in high glucose-induced mesangial cells to protect against DN. The medicine such as *Betulinic acid* derived from the bark of the white birch tree^[57] and *Polydatin* derived from *Polygonum cuspidatum* Sieb. et Zucc^[58] have been reported to ameliorate DN renal inflammation *via* inhibiting the activation of NF- κ B signaling pathway and decreasing inflammatory cytokines both *in vivo* and *in vitro*. Furthermore, *Brazilin* (a compound derived from *Caesalpinia sappan*)^[59], *Notoginsenoside R1* (a major component of *Panax notoginseng*)^[60] and *Paecilomyces hepialid* (a derivative from *Cordyceps sinensis*)^[61] inactivates NF- κ B, suppress inflammatory cytokines TNF- α , TGF- β 1, IL-1 and IL-6, and increase the levels of the anti-inflammatory factor IL-10 in db/db mice or STZ-induced diabetic nephropathy rats. In addition, *Liquiritigenin*, one flavonoid compound of *liquiritin*, has been shown to reduce expressions and secretion of IL-6 and IL-1 β through NF- κ B pathway and NLRP3 inflammasome in high glucose-induced glomerular mesangial cells^[62].

2.1.2 Effect on Nrf2 pathway

Nrf2 plays an important role of regulating the cellular antioxidant response to counteract renal damage in diabetes. *Hesperetin* ameliorates diabetic nephropathy inflammatory responses by activating Nrf2/anti-oxidant response element (ARE)/glyoxalase 1 pathway and declining IL-1 β and TNF- α in STZ rats^[63]. *Digitoflavone* also has anti-oxidative and anti-inflammatory effects on mediating Nrf2 activation to improve renal performance in Nrf2^{+/+} and Nrf2^{-/-} mice, STZ-induced diabetic rats and SV40-transformed mouse mesangial cells^[64]. Moreover, *6-Shogaol* (6-SG)^[65], *Carnosic acid*^[66], the ethanol extract of *Ligusticum chuanxiong rhizome*^[67], and *Schizandrin B*^[68] have been shown anti-inflammatory effects on activating Nrf2 and inhibiting NF- κ B pathway to improve DN inflammation in

diabetic mice and *vitro*.

2.1.3 Effect on multiple pathways

Chinese medicine, as a therapeutic approach targets multiple signaling pathways or organs to improve the whole internal environment of DN. Astilbin, a flavonoid isolated from many herbs such as the rhizome of *Smilax china* L. (Smilacaceae), attenuates inflammation and ECM accumulation *via* inhibiting the TLR4/MyD88/NF- κ B pathway in HG-induced rat glomerular mesangial cells^[69]. Similarly, Tripterygium glycosides tablet, isolated from *Tripterygium wilfordii* Hook F recognized as a treatment for autoimmune disorders^[70], ameliorates DN kidney by inhibition of TLR4/NF- κ B signaling and downregulation of inflammatory mediator IL-1 β , and MCP-1 in high-fat diet/STZ-induced diabetic rats^[71]. Besides, polysaccharides from *Liriodendron Radix*^[72] and Salvianolic acid from *Salvia miltiorrhiza* Bunge^[73] both inhibit NF- κ B and p38 MAPK signaling pathways and regulate inflammatory cytokines to alleviate diabetic renal inflammation in STZ-diabetic rats or kidneys of 5/6Nx rats. Interestingly, Oridonin, isolated from *Rabdosia rubescens*, attenuates diabetes-induced renal injury, decreased urinary protein excretion levels and alleviates infiltration of inflammatory cells (cluster of differentiation 68) in rats. And it also reduces the levels of pro-inflammatory cytokines including TNF- α , IL-6, IL-1 β and MCP-1 may be ascribed to TLR4/p38-MAPK and TLR4/NF- κ B signaling pathways both *in vivo* and *in vitro*^[74]. Taxifolin (TA), a common flavonoid in Pinaceae tree, alleviates kidney of STZ-induced DN possibly *via* Caveolin-1/NF- κ B pathway^[75]. Berberine effectively inhibits RhoA/ROCK signaling activation in diabetic rat kidneys and high glucose-induced glomerular mesangial cells (GMCs) and simultaneously down-regulates NF- κ B activity, accompanied by reduction of intercellular adhesion molecule-1 to ameliorate renal inflammation in DN^[76]. *Ramulus mori* polysaccharides exhibit renoprotection of DN associated with inflammation reaction through blocking the IL-1/NF- κ B pathway and reducing proinflammatory cytokines such as IL-6, interferon- γ (IFN- γ) and TNF- α in STZ-induced mice^[77]. Whereas, *Pueraria tuberosa* extract plays anti-inflammatory role in downregulation of PKC- α and NF- κ B pathway and normalizing the expression of inflammatory cytokines IL-6 and TNF- α and iNOS in the kidney of STZ-induced DN rats^[78]. In addition,

Panax notoginseng saponins could protect kidney from diabetes with the possible mechanism of up-regulating SIRT1 and suppressing NF- κ B p65, therefore inhibiting inflammation through decreasing the induction of inflammatory cytokines MCP-1 and TGF- β 1 in alloxan-induced rats and rat mesangial cells^[79].

In particular, Curcumin expresses various anti-inflammation effects in DN. Curcumin inhibits the activity of NF- κ B and as a result decreases the expression of inflammatory cytokines TNF- α and IL-1 β , chemokine MCP-1 and adhesion molecule ICAM-1 to ameliorate macrophage infiltration in streptozotocin induced-diabetic nephropathy rats^[80]. Furthermore, curcumin enhances Nrf2 system and inhibits inflammatory signaling resulting in attenuating urinary excretion of albumin in patients with T2DM to ablate DN progress^[81]. In addition, it also ameliorates renal inflammatory response in DN *via* reversing caveolin-1 Tyr14 phosphorylation influenced TLR4 activation in STZ-induced diabetic rats and high glucose (HG)-induced podocyte^[82].

Another multi-effect medicine Ellagic acid regulates oxidative stress and inflammatory *via* inhibiting HMGB1-TLR4-NF- κ B pathway to attenuate streptozotocin induced diabetic nephropathy^[83]. Ellagic acid also exhibits attenuation of renal inflammatory processes *via* inhibition of NF- κ B pathway and reduction of pro-inflammatory cytokines IL-1 β , IL-6 and TNF- α in HFD/STZ-induced type 2 diabetic Wistar albino rats and rat NRK 52E proximal tubular epithelial cells^[84].

Paeony is also well investigated by a wide range of studies. Total glucosides of paeony have anti-inflammatory and immuno-regulatory effects, which inhibits the expression of TLR2 and 4, NF- κ B p65, TNF- α and IL-1 and decreases the levels of 24 h urinary albumin excretion rate in diabetic rats kidneys^[85]. Paeoniflorin, the primary component of total glucosides of paeony, improves the inflammatory status of DN by inhibiting the TLR2-MyD88- NF- κ B pathway and regulating iNOS, TNF- α , IL-1 β , and MCP-1 in streptozotocin-induced wild-type littermates mice and TLR2 knockout mice (TLR2-/-)^[86]. It also affects macrophage infiltration and activation through TLR4 pathway, further decreases iNOS and inflammatory factors in STZ-induced diabetic mice kidney^[87]. Moreover, Paeoniflorin inhibits activation of TLR2/4, reduces

MyD88, p-IRAK1, p-IRF3, and NF- κ B p65 preventing macrophage activation, which in turn alleviates inflammation and ultimately improves DN in db/db mice and RAW264.7 cells^[88], while attenuates renal lesions associated with inhibition of the JAK2/STAT3 signaling pathway as well as regulation macrophage infiltration and inflammatory factors MCP-1, TNF- α and IL-1 β in STZ-induced

type 1 diabetic mice^[89].

Meanwhile, Resveratrol attenuates inflammation and renal mesangial cell proliferation *via* inhibition of Akt/NF- κ B pathway to protect DN^[90]. It also protects diabetic kidney by modulation of oxidative stress and inflammatory cytokines *via* Nrf2 – Keap1 signaling or AMP-activated protein kinase in STZ-induced rats^[91-92].

Table 1 Chinese herbal medicine mediated innate immunity–transcription factors and protein kinases in DN

Name	Origins	DN model	Mechanisms	Pathways	Ref.
<i>Jiangtang</i> decoction	Euphorbia humifusa Willd, S. miltiorrhiza Bunge, A. mongholicus Bunge, A. asphodeloides Bunge, and C. chinensis Franch	KK-Ay mice	ICAM-1, TNF- α , and IL-6 ↓	NF- κ B pathway	[38]
<i>Tang shen</i> formula	Radix puerariae, astragalus, Ligustrum lucidum, Lucid ganoderma, Salvia miltiorrhiza and Rheum rhabarbarum	High-fat diet/STZ-induced diabetic rats	MIF and MCP-1 ↓	SIRT1/NF- κ B pathway	[39]
Another <i>Tang shen</i> formula	Astragalus root, burning bush twig, rehmannia root, bitter orange, cornus fruit, rhubarb root and rhizome, notoginseng root	High-fat diet/STZ-induced diabetic rats	TNF- α and IL-1 β ↓ MCP-1 ↓	NF- κ B pathway	[40]
<i>Xiexin</i> decoction	Rhizoma Coptidis alkaloids, Radixet Rhizoma Rhei polysaccharides, and Radix Scutellaria flavones	High-fat diet/STZ-induced diabetic rats Db/db mice HG-induced rat mesangial cells	MCP-1, TNF- α , and IL-6 ↓ TNF- α and IL-1 β , ICAM-1, and MCP-1 ↓	NF- κ B pathway	[41–42]
Calycosin	Radix astragali	Db/db mice Mouse tubular epithelial cells	AGEs ↓ TNF- α and IL-1 β ↓	NF- κ B pathway	[43]
Aqueous extract of <i>Portulaca oleracea</i>	<i>Portulaca oleracea</i>	Db/db mice	AGEs and ICAM-1 ↓	NF- κ B pathway	[44]
Aqueous extract of <i>Prunella vulgaris</i>	<i>Prunella vulgaris</i>	Human mesangial cell	NF- κ B ↓ ICAM-1 and MCP-1 ↓		[45]
Andrographolide	<i>Andrographis paniculata</i>	High-fat diet/STZ-induced mice	NOX1 ↓ ROS and TNF- α ↓	Akt/NF- κ B signaling pathway	[46]
Morroniside	<i>Corni Fructus</i>	db/db mice	ROS ↓ NF- κ B ↓		[47]
<i>Danshen</i> injection	<i>Salvia miltiorrhiza</i>	STZ-induced diabetic rats	SOD ↑, ROS and MDA ↓ TNF- α , IL-1 β and IL-6 ↓	I κ B/NF- κ B signaling pathway	[49]
Lycium barbarum polysaccharides	Lycium barbarum	Alloxan-induced diabetic rabbits	MCP and ICAM-1 ↓ NF- κ B and AngII ↓		[50]
Mangiferin		STZ-induced diabetic rats	NF- κ B ↓, IL-1 β ↓		[51]

Continued to Table 1					
Name	Origins	DN model	Mechanisms	Pathways	Ref.
Geniposide		STZ-induced diabetic rats	ICAM-1, TNF- α , IL-1 β and IL-6 $\downarrow$ Monocytes and T lymphocytes infiltration $\uparrow$	NF- κ B pathways	[52]
Ruscogenin	Ruscus aculeatus	STZ-induced diabetic rats	ICAM-1 and MCP-1 $\downarrow$	NF- κ B pathway	[53]
Astragaloside IV	Astragalus membranaceus	STZ-induced diabetic rats	TNF- α , MCP-1 and ICAM-1 $\downarrow$	NF- κ B pathway	[54]
Coreopsis tinctoria Nutt	Coreopsis tinctoria Nutt	HG-induced rat mesangial cells	MCP-1 $\downarrow$	NF- κ B pathway	[55]
Quercetin		HG-induced human mesangial cell	MCP-1 $\downarrow$	NF- κ B pathway	[56]
Betulinic acid	The bark of the white birch tree	STZ-induced diabetic rat HG-treated glomerular mesangial cells		NF- κ B pathway	[57]
Polydatin	Polygonum cuspidatum Sieb. et Zucc	Rat glomerular mesangial cells	ICAM-1 and TGF- β $\downarrow$	NF- κ B pathway	[58]
Brazilin	Caesalpinia sappan	Db/db mice	NF- κ B p65 $\downarrow$ Pro-inflammatory cytokines and chemokines $\downarrow$ IL-10 $\uparrow$		[59]
Notoginsenoside R1	Panax notoginseng	STZ-induced diabetic rats	TNF- α , TGF- β 1, IL-1 and IL-6 $\downarrow$ IL-10 $\uparrow$	NF- κ B pathway	[60]
Paecilomyces hepialid	Cordyceps sinensis	High-fat diet/STZ-induced diabetic rats	TNF- α , IL-2, IL-6, and IL10 $\downarrow$	NF- κ B pathway	[61]
Liquiritigenin	liquiritin	High glucose-induced glomerular mesangial cells	MDA and NOX4 $\downarrow$ SOD $\uparrow$ IL-6 and IL-1 β $\downarrow$	NF- κ B and NLRP3 inflammasome pathways	[62]
Hesperetin		STZ rats	IL-1 β and TNF- α $\downarrow$	Nrf2/ARE/glyoxalase 1 pathway	[63]
Digitoflavone		Nrf2 $^{+/+}$ and Nrf2 $^{-/-}$ mice by STZ-induced diabetic rats SV40-transformed mouse mesangial cells	ROS $\downarrow$	Nrf2 pathway	[64]
6-Shogaol	Gingerols	Db/db mice	NF- κ B $\downarrow$ MCP-1, TNF- α , and IL-6 $\downarrow$ Nrf2 $\uparrow$		[65]
Carnosic acid		HG-induced mice glomerular mesangial cells	Nrf2 $\uparrow$	NF- κ B pathway	[66]

Continued to Table 1

Name	Origins	DN model	Mechanisms	Pathways	Ref.
The ethanol extract of Ligusticum chuanxiong rhizome	Ligusticum chuanxiong rhizome	STZ-induced C57BL/6 mice Human renal glomerular endothelial cells RAW 264.7 murine macrophages		Nrf2/NF- κ B pathway	[67]
Schizandrin B	Schisandra chinensis	STZ-induced diabetic mice		Nrf2/NF- κ B pathway	[68]
Astilbin	Rhizome of Smilax china L.	HG-induced rat glomerular mesangial cells	ECM accumulation ↓	TLR4/MyD88/NF- κ B pathway	[69]
Tripterygium glycosides tablet	Tripterygium wilfordii Hook F	High-fat diet/STZ-induced diabetic rats	IL-1 β and MCP-1 ↓	TLR4/NF- κ B pathway	[71]
Polysaccharides	Liriodendron Radix	STZ-induced diabetic rats	TNF- α and IL-6 ↓	NF- κ B pathways	[72]
Salvianolic acid A	Salviae miltiorrhizae Bunge	5/6Nx rats	TNF- α , and IL-1 β ↓ MCP-1, ICAM-1, and VCAM-1 ↓	NF- κ B/p38 MAPK pathways	[73]
Oridonin	Rabdosia rubescens	<i>Vivo and in vitro</i>	TNF- α , IL-6, IL-1 β and MCP-1 ↓	TLR4/p38-MAPK TLR4/NF- κ B pathways	[74]
Taxifolin	Pinaceae tree	STZ-induced diabetic rats		Caveolin-1/NF- κ B pathway	[75]
Berberine	Berberis	Diabetic rat kidneys HG-induced glomerular mesangial cells	NF- κ B activity ↓ ICAM-1 ↓	RhoA/ROCK pathway	[76]
Ramulus mori polysaccharides	Ramulus mori	STZ-induced diabetic mice	IL-6, interferon- γ (IFN- γ) and TNF- α ↓	IL-1/NF- κ B pathway	[77]
Pueraria tuberosa extract	Pueraria tuberosa	STZ-induced diabetic rats	IL-6 and TNF- α and iNOS ↓	PKC- α and NF- κ B pathway	[78]
Panax notoginseng saponins	Panax notoginseng	Alloxan-induced rats Rat mesangial cells	MCP-1 and TGF- β 1 ↓	SIRT1/NF- κ B pathway	[79]
Curcumin	Curcuma longa	STZ-induced diabetic rats Patients HG-induced podocyte	TNF- α , IL-1 β , MCP-1 and ICAM-1 ↓ Nrf2 ↑ Urinary excretion of albumin ↓	NF- κ B pathway TLR4 pathway	[80–82]
Ellagic acid		STZ-induced diabetic rats HFD/STZ-induced type 2 diabetic Wistar albino rats Rat NRK 52E proximal tubular epithelial cells	TNF- α and serum creatinine ↓ IL-1 β , IL-6 and TNF- α ↓	HMGB1-TLR4-NF- κ B pathway NF- κ B pathway	[83–84]
Total glucosides of paeony	Paeony	TLR2 and 4, NF- κ B p65 ↓	TNF- α and IL-1 ↓		[85]

Continued to Table 1

Name	Origins	DN model	Mechanisms	Pathways	Ref.
Paeoniflorin	Paeony	STZ-induced wild-type littermates mice and TLR2 knockout mice STZ-induced diabetic mice Db/db mice RAW264.7 cells STZ-induced type 1 diabetic mice	iNOS, TNF- α , IL-1 β , and MCP-1 $\downarrow$ TLR2/4, MyD88, p-IRAK1, p-IRF3, and NF- κ B p65 $\downarrow$ MCP-1, TNF- α and IL-1 β $\downarrow$	TLR2-MyD88- NF- κ B pathway TLR4 pathway JAK2/STAT3 pathway	[86–89]
Resveratrol		Rat mesangial cell and STZ-induced type 1 diabetes mice STZ-induced diabetic rats	PAI-1 and ICAM-1 $\downarrow$ IL-1 β $\downarrow$ TNF- α , IL-1 β , IL-6 and NF- κ B p65 subunit $\downarrow$	Akt/NF- κ B pathway Nrf2-Keap1 pathway AMP-activated protein kinase	[90–92]

2.2 Effect on inflammatory mediators

Growing evidence highlights the key factor of inflammatory mechanisms in the development and progression of DN. Therefore, anti-inflammatory strategies of Chinese herbal medicines mediating inflammatory mediators (chemokines, cytokines, and adhesion molecules) may offer new approaches to attenuate renal injury. Following mentioned Chinese medicines in the review are shown in Table 2.

2.2.1 Chemokines and cytokines

Chemokines and cytokines have been reported to play a key role in the pathogenesis of DN. Many studies show that Rich-Polyphenols Extract of *Dendrobium loddigesii* [93], Mulberry leaf powder [94], and the flavonoids from *Pyrrosiae folium* improves [95] improve diabetic nephropathy through decreasing expression of inflammatory cytokines IL-6 and TNF- α in diabetic mice and rats. Both *Allium tuberosum* [96] and *Lycium chinense* leaf extract [97] suppress pro-inflammatory parameters TNF- α , IL-6 and IL-1 β , and oxidative stress in STZ-induced DN rats. MCP-1 mediates the migration of monocytes and macrophages into kidney tissue. Triptolide purified from *Tripterygium wilfordii* Hook F, attenuates renal inflammatory reaction through reducing chemokine MCP-1 in db/db diabetic mice [98] and urinary MCP-1 in DN patients [99]. Besides, Mori cortex prevents kidney damage through inhibiting expression of inflammatory cytokine TNF- α and chemokine MCP-1 in streptozocin-induced diabetic rat glomerulus [100].

Additionally, total flavones of *Abelmoschus manihot* downregulate proinflammatory cytokines TNF- α , IL-6 and MCP-1 and exerts anti-inflammatory effects significantly through inhibiting the activation of iRhom2/TACE signaling *in vivo* and *in vitro* [101]. Nevertheless, *Trichosanthes kirilowii* lectin could increase the anti-inflammation production of IL-10 and arginase-1(Arg-1), and decrease the production of TNF- α and iNOS to inhibit renal inflammation in STZ-induced diabetic rats [102].

2.2.2 Adhesion molecules

Adhesion molecules mediate cell adhesion associated with leukocyte infiltration and disease progression of DN. Puerarin, component extracted from the rhizome of *Pueraria lobata*, suppresses TNF- α and ICAM-1 to improve early-stage renal damage in STZ diabetic rats [103]. Besides, Acetylshikonin (main ingredient of *Zicao*) [104] and Esculin (extracted from *Fraxinus rhynchophylla*) [105], decreases the expressions of inflammatory mediators including ICAM-1, IL-1 β , IL-6, MCP-1 and infiltration of macrophages to ameliorate inflammation responses and renal injury in diabetic mice and rats. Moreover, Moutan Cortex ameliorates the inflammation through decreasing ICAM-1 and TGF- β 1 in AGEs-induced mesangial cells and DN rats [106], while Terpene glycoside component from Moutan Cortex attenuates ER stress-related inflammation in the pathogenesis of DN, associated with the inhibition of IRE1/NF- κ B activation in turn reduce the expression of ICAM-1

IL-6, and MCP-1 *in vivo* and *in vitro*^[107]. In addition, Xueshuantong for Injection suppresses the overexpression of inflammation mediators including TNF- α , IL-6, IL-1 β , inducible nitric oxide synthase (iNOS) and ICAM-1 and blocks TGF- β /Smad2/3 signaling pathway to improve renal damage in STZ-induced diabetic rats^[108]. Similarly, Xiao-Shen-Formula granules, consisted of tuckahoe (16.7%), radix astragali (16.7%), red paeonia (11.1%), luffa (8.3%), honeysuckle flower (11.1%), radix curcumae (8.3%), cogongrass rhizome (16.7%), and radix achyranthis bidentatae (11.1%), have been proved to

prevent inflammation in DN model through TNF- α involved signaling, ICAM1 and VCAM1 participated in inflammatory Reaction of cultured human glomerular endothelial cell (hGECs)^[109].

2.2.3 NLRP3 inflammasome

The NLRP3 inflammasome mediate a form of inflammatory cell death in the pathogenesis of DN. Ophiocordyceps sinensis^[110], Luteolin^[111-112] and Naringin^[113] have been reported to modulate NLRP3 inflammasome and downstream effectors IL-1 β /IL-18 both in diabetic rats or vitro to alleviate the inflammatory reaction in DN.

Table 2 Chinese herbal medicines mediated inflammatory mediators in DN

Name	Origins	DN model	Mechanisms	Ref.
Rich-Polyphenols Extract of Dendrobium loddigesii	Dendrobium loddigesii	Db/db mice	TNF- α and IL-6 ↓	[93]
Mulberry leaf powder	Mulberry		TNF- α and IL-6 ↓	[94]
The flavonoids from Pyrrosiae folium	Pyrrosiae folium	High-fat diet/STZ-induced diabetic rats	IL-6, TNF- α and IL-1 β ↓	[95]
Allium tuberosum	Allium tuberosum	High-fat diet/STZ-induced diabetic rats	TNF- α , IL-6 and IL-1 β ↓ MDA, GSH, CAT and SOD ↓	[96]
Lycium chinense leaf extract	Lycium chinense	STZ-induced diabetic rats	GSH, SOD, CAT, MDA, TNF- α , IL-6 and IL-1 β ↓	[97]
Triptolide	Tripterygium wilfordii Hook F	Db/db mice DN Patients	MCP-1 ↓ Urinary MCP-1 ↓	[98–99]
Mori cortex	Mori cortex	STZ-induced diabetic rats	TNF- α and MCP-1 ↓	[100]
Total flavones of Abelmoschus manihot downregulates	Abelmoschus manihot downregulates	STZ-induced Sprague-Dawley rats Human proximal tubule epithelial cells Human renal mesangial cells	TNF- α , IL-6 and MCP-1 ↓	[101]
Trichosanthes kirilowii lectin	Trichosanthes kirilowii	STZ-induced diabetic rats	TNF- α and iNOS ↓ IL-10 and Arg-1 ↓	[102]
Puerarin	Rhizome of Pueraria lobate	STZ-induced diabetic rats	TNF- α and ICAM-1 ↓	[103]
Acetylshikonin	Zicao	STZ-induced diabetic mice	IL-1 β , IL-6, MCP-1 ↓ ICAM-1 and infiltration of macrophages ↓	[104]
Esculin	Fraxinus rhynchophylla	STZ-induced diabetic rats	IL-1, IL-6, ICAM-1 and NO levels ↓	[105]
Moutan Cortex	Moutan Cortex	High-fat diet/STZ-induced diabetic rats	IL-6, MCP-1, TGF- β 1, ICAM-1 ↓	[106]

Continued to Table 2				
Name	Origins	DN model	Mechanisms	Ref.
Terpene glycoside	Moutan Cortex	Vivo and vitro	IL-6, MCP-1, and ICAM-1 ↓ IRE1/NF-κB activation ↓	[107]
Xueshuantong Injection	Panax Notoginseng	STZ-induced diabetic rats	TNF-α, IL-6, IL-1β ↓ iNOS and ICAM-1 ↓	[108]
Xiao-Shen-Formula granules	Tuckahoe, radix astragali, red paeonia, luffa, honeysuckle flower, radix curcumae, cogongrass rhizome, and radix achyranthis bidentatae	Human glomerular endothelial cells	TNF-α, ICAM1, VCAM1, MCP-1 ↓	[109]
Ophiocordyceps sinensis	Ophiocordyceps sinensis	High-fat diet/STZ-induced diabetic rats	P2X7R/NLRP3 inflammasome ↓ IL-1β/IL-18 ↓	[110]
Luteolin		HG-induced MPC-5 cells	NLRP3 inflammasome formation ↓ IL-1β ↓	[112]
Naringin	Grapefruit and other related citrus species	HG-induced rat mesangial cells	NLRP3 inflammasome ↓ IL-1β/IL-18 ↓	[113]

3 Conclusions

The number of type 2 diabetes patients worldwide was estimated to reach to 510.8 million in 2030^[114], foreshadowing a commensurate increase in DN. Emerging evidence of immune responses and inflammation as key pathogenicity relating aberrant metabolism to DN provides new opportunities. Chinese herbal medicines have involved glycemic control and renal protection such as reduction of proteinuria with less toxicity in DN patients for long time. Development of inflammatory biomarkers and application of molecular biology increase concern of Chinese herbal medicines for treatment of inflammation in DN. In this paper, the underlying mechanism studies of Chinese herbal medicines mediating inflammation mostly focus on monomers from single herbal medicines or extracts of herbs, as well as few researches on herbal formulas. Moreover, these results investigated the anti-inflammatory effects of Chinese medicines on diabetic nephropathy in diabetic animal and cell line models. To translate the therapeutic potentials for DN into reality, placebo-controlled and randomized controlled clinical trials of Chinese medicines are needed in the future, and then the meaningful reduction in the burden of DN will finally be hit.

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中草药干预糖尿病肾病炎症的作用*

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摘要 随着糖尿病发病率逐年升高, 糖尿病肾病成为导致慢性肾脏疾病和终末期肾脏疾病的主要原因. 而目前控制血糖及抑制肾素-血管紧张素系统的药物治疗, 并不能有效防止糖尿病肾病进展. 近年来发现, 慢性低水平炎症和免疫系统激活在糖尿病性肾病的发生及发展中起着至关重要的作用. 明确糖尿病肾病进展中的炎症机制将有助于确定新的潜在靶点及研发抗炎治疗策略. 越来越多的证据表明, 中药治疗可以有效改善糖尿病性肾病的高血糖和蛋白尿, 并能延缓其进展成为终末期肾病. 糖尿病肾病动物实验和体外研究证实中药复方、中草药提取物和中药单体具有调节炎症介质的作用. 本文旨在归纳总结文献中与糖尿病肾病肾损伤相关的炎症分子和途径, 并探讨中草药靶向抗炎治疗糖尿病肾病的作用.

关键词 糖尿病肾病, 炎症, 中草药

中图分类号 R259

DOI: 10.16476/j.pibb.2020.0188

* 中医药防治慢性病国际合作基地(GZYYGJ2019034)和中医药防治糖尿病国际联合研究中心(2015B01022)及北京市国际科技合作基地资助项目.

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收稿日期: 2020-06-02, 接受日期: 2020-06-10