Review Article

Review of Herbal Traditional Chinese Medicine for the Treatment of Diabetic Nephropathy

Guang-dong Sun, Chao-yuan Li, Wen-peng Cui, Qiao-yan Guo, Chang-qing Dong, Hong-bin Zou, Shu-jun Liu, Wen-peng Dong, and Li-ning Miao

Department of Nephrology, Second Hospital of Jilin University, Changchun 130041, China

Correspondence should be addressed to Guang-dong Sun; sungd@jlu.edu.cn and Li-ning Miao; miaolining55@163.com

Received 28 May 2015; Accepted 22 July 2015

Academic Editor: David W. Powell

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Diabetic nephropathy (DN) is the most serious chronic complications of diabetes; 20–40% of diabetic patients develop into end stage renal disease (ESRD). However, exact pathogenesis of DN is not fully clear and we have great difficulties in curing DN; poor treatment of DN led to high chances of mortality worldwide. A lot of western medicines such as ACEI and ARB have been demonstrated to protect renal function of DN but are not enough to delay or retard the progression of DN; therefore, exploring exact and feasible drug is current research hotspot in medicine. Traditional Chinese medicine (TCM) has been widely used to treat and control diabetes and its complications such as DN in a lot of scientific researches, which will give insights into the mechanism of DN, but they are not enough to reveal all the details. In this paper, we summarize the applications of herbal TCM preparations, single herbal TCM, and/or monomers from herbal TCM in the treatment of DN in the recent 10 years, depicting the renal protective effects and the corresponding mechanism, through which we shed light on the renal protective roles of TCM in DN with a particular focus on the molecular basis of the effect and provide a beneficial supplement to the drug therapy for DN.

1. Introduction

Diabetic nephropathy (DN) is a widely recognized microvascular complication of diabetes and almost the leading cause of end-stage kidney failure worldwide responsible for morbidity and mortality [1]. Clinical manifestations of DN include initial increase in glomerular filtration (GFR), proteinuria, increased creatinine levels, and eventually decreased GFR [2–4]. Major pathological changes of DN are virtually indistinguishable in both type 1 and type 2 diabetes, including mesangial expansion, extracellular matrix (ECM) accumulations, tubulointerstitial fibrosis, and glomerular sclerosis. Hyaline arteriolar sclerosclerosis is often prominent in the established DN pathological features caused by endothelial dysfunction and inflammation [5–7].

Multiple factors have been implicated in the pathogenesis of DN including hyperglycemia induced activation of advanced glycation end products (AGEs) and reactive oxygen species (ROS); JAK-STAT pathways and G protein signaling; activation of the PKC, renin-angiotensin aldosterone system (RAAS), transforming growth factor β-Smad-mitogen-activated protein kinase (TGF-β-Smad-MAPK), deregulated expression of cyclin dependent kinases (CDK), and their inhibitors; and aberrant expression of ECM proteins, ECM-degrading enzymes, metalloproteinases, and their inhibitors [8]. The abovementioned factors can induce aberrant expression of profibrotic and proinflammatory cytokines, cell-cycle genes, and ECM genes involved in DN [9]. A large number of novel treatment options has arisen from experimental studies based on the pathogenic factors of DN, including intensive glycemic control, precise blood pressure control, optimal RAAS blockade with ACEI/ARB, life style modifications such as exercise and dietary restrictions, and a lot of novel agents [10], but the portion of ESRD due to DN still remains high in spite of the widespread application of numerous therapeutic approaches focusing on the management of factors mentioned above [11–13]. Therefore, interventions that could effectively delay the progression of DN are greatly required.

In China, traditional Chinese medicine (TCM) has been widely used in the treatment of diabetes and its complications
2. Applications of TCM in DN

Plants have been widely used for medical purposes long before recorded history [18]. In China, TCM emerged and influenced the surrounding countries such as Japan and South Korea; increasing popularity of TCM caused great interests in laboratory and clinical investigations in lots of diseases on its efficiency and action mechanism. TCM manifests as herbal medicine, acupuncture, moxibustion, massage, dietary therapy, and physical exercise including shadow boxing and Qigong, and herbal remedies are the focus of TCM in mainland China [19] and acupuncture is prevalent in the United States [18]. Under the urgent need for the treatment of DN, we focus on the update of the efficient herbal TCM preparations, single herbal TCM, and/or monomers from herbal TCM in DN related clinical and experimental trials, through which we explore the effective herbal TCM for DN and clearly put forward underlying mechanism in the treatment of DN.

2.1. TCM Preparations in DN. TCM preparations are applied as decoction, pill, and capsule in the treatment of DN. We will introduce the TCM preparations in alphabetical order about components of TCM preparations, therapeutic effects in clinical or experimental studies, and relevant mechanism. All the mentioned TCM preparations in this review are listed in Table 1.

2.1.1. Chaihuang Yishen Granule (CHYS). Chaihuang Yishen granule (CHYS, also called Qilong-Lishui granule) is composed of radix astragali, Dioscorea nipponica, radix bupleuri, Angelica sinensis, Pyrrosia petiolosa, Polyporus umbellatus, and Hirudo nipponica. A recent study in STZ plus uninephrectomized induced rats showed that CHYS could be a therapeutic agent for DN by blocking TGF-β1/Smad3-mediated renal fibrosis [20].

2.1.2. Compound Rhizoma Coptidis Capsule (CRCC). Compound rhizoma coptidis capsule (CRCC) is composed of rhizoma coptidis, Kudzu root, dwarf lilyturf, and Loquat leaf. CRCC has been shown to protect renal function and slow down the progression of DN by the suppression of TGF-β1 and type IV collagen expression in STZ induced diabetic rats [21].

2.1.3. Compound Shenhua Tablet (CST). Compound Shenhua Tablet (CST), is composed of radix astragali, fructus ligustri lucidi, rhizoma zedoaria, and honeysuckle. CST treatment in STZ induced diabetic rats showed that urine mAlb, Scr, BUN, Glu, TG, and TC were significantly lower than the diabetic model group [22].

2.1.4. Danggui Buxue Tang (DBT). Danggui buxue tang (DBT), a preparation including radix astragalii and radix Angelica sinensis, has been shown to partially attenuate the increases in blood glucose, TG, and CHO, and DBT was supposed to retard DN progression by suppressing TGF-β1 expression in STZ induced diabetic rats [23]. In the HG stimulated glomerular mesangial cells, DBT could inhibit cell proliferation and expression of LN, FN, and collagen IV indicating the renoprotective effect of DBT on DN at the early stages [24].

2.1.5. Danggui Shaoyao San (DSS). Danggui Shaoyao San (DSS) is a famous TCM formula comprising six herbal medicines: radix Paeniae Alba, radix Angelica sinensis, rhizoma Chuanxiong, Poria cocos, rhizoma Atractylodis macrocephala, and rhizoma Alismatis. DSS has been shown to protect renal function in STZ induced diabetic rats through regulating plasma glucose and attenuating AGEs expression in diabetic glomeruli [25].

2.1.6. Fufang Xue Shuan Tong (FXST). Fufang Xue Shuan Tong (FXST) capsule is composed of radix notoginseng, Salvia miltiorrhiza, XuanShen, and radix astragali and has been used to treat DN for many years. High dose of FXST treatment could prevent glomerular hypertrophy and mesangial matrix expansion through regulation of oxidative stress including increasing SOD activities and decreasing MDA levels in the kidney of HFD-fed plus STZ induced rats [26].

2.1.7. Hachimijiogan (HJG). A most popular herbal medicine in Japanese Kampo, Hachimijiogan (HJG, Ba Wei Di Huang Tong in Chinese), is extracted from a mixture of Rehmannia radix, corni fructus, Dioscorea rhizome, Hoelen, Alismatis rhizome, Moutan cortex, Cinnamomi cortex, and Aconiti tuber. In subtotal nephrectomy plus STZ induced rats, HJG could reduce blood glucose and urinary protein excretion levels and increase Ccr; furthermore, HJG could ameliorate oxidative stress and AGEs formation associated with DN and subsequently prevent the development of renal lesions including glomerular sclerosis, tubulointerstitial lesions, mesangial expansions, and atherosclerosis [27]. In spontaneous diabetic WBN/Kob rats with DN, HJG could prevent DN progression through several established biomarkers in plasma [28] and by reducing renal oxidative injury and expression of FN and TGF-β1 proteins [29]. In OLETF rats, HJG could reduce TGF-β1, FN, iNOS, and COX-2 expressions in kidney cortex, urinary protein excretion was decreased, Ccr levels were improved, and serum glycosylated protein and AGEs were reduced effectively; data mentioned above suggested that HJG has beneficial effect on the DN progression [30].

2.1.8. Hu-Lu-Ba-Wan (HLBW). Hu-Lu-Ba-Wan (HLBW), composed of Trigonella foenum-graecum L. (TFG) and Poriae corylifolia L. (PC), has been shown to improve hyperglycemia, hyperlipidemia, and proteinuria in the HFD-fed plus STZ induced rats and could play renoprotective effect in attenuating renal oxidative stress via PKC-α/NADPH oxidative pathway [31].
Table 1: Applications of herbal TCM Preparations in DN.

| Name   | Origins                                                                 | Methods                                      | Results                                                                                                                                  | Pathways                                                                 |
|--------|-------------------------------------------------------------------------|----------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------|
| CHYS   | Radix astragali, Dioscorea nipponica, radix bupleuri, Angelica sinensis, Pyrosia petiolaris, Polyporus umbellatus, and Hirudo nipponica | Type 1 diabetic animal study (STZ + nephrectomized rat) | Inhibiting 24 h proteinuria and progressive renal fibrosis (glomerulosclerosis index, tubulointerstitial fibrosis index, and upregulation of ECM), upregulating Smad7, and downregulating TGF-β1, TGF-βR, Smad3 activation, and miRNA-21 | [20]                                                                     |
| CRCC   | Rhizoma coptidis, Kudzu root, dwarf lilyturf, and loquat leaf           | Type 1 diabetic animal study (STZ induced rats) | Reducing FBG, BUN, Cr, Upro levels and TGF-β1, and collagen IV expressions and alleviating pathological lesions of kidney | Through TGF-β1 pathway [21]                                              |
| CST    | Radix astragali, fructus ligustri lucidi, Rhizoma zedoaria, and honeysuckle | Type 1 diabetic animal study (STZ induced rats) | Decreasing urine mAlb, Scr, BUN, Glu, TG, and TC                                                                                       | [22]                                                                     |
| DBT    | Angelica sinensis and Astragalus membranaceus                           | Type 1 diabetic animal study (STZ induced rats) | Attenuating the increases in blood glucose, TG and CHO, and TGF-β1 expression in kidney Inhibit cell proliferation and expression of LN, FN, and collagen IV | Through TGF-β1 way [23, 24]                                              |
| DSS    | Radix Paeoniae Alba, radix Angelica sinensis, rhizoma Chuanxiong, Poria cocos, rhizoma Atractylodis macrocephala, and Alismatis rhizome | Type 1 diabetic animal study (STZ induced rats) | Decreasing FBG and attenuating AGES expression in diabetic glomeruli Through modulating oxidative stress via AGES expression [25] |                                                                                            |
| FXST   | SanQi, DanShen, XuanShen, and HuangQi                                   | Type 2 diabetic animal study (HFD + STZ induced rats) | Preventing glomerular hypertrophy and mesangial matrix expansion Through regulating oxidative stress [26] |                                                                                            |
| HJG    | Rehmanniae radix, Corni fructus, Dioscorea rhizome, Hoelen, Alismatis rhizome, Moutan cortex, Cinnamomi cortex, and Aconiti tuber | Type 1 diabetic animal study (STZ + nephrectomized rat) | Reducing blood glucose and urinary protein excretion and increasing creatinine clearance, ameliorating oxidative stress and AGES formation associated with DN, and preventing the development of renal lesions including glomerular sclerosis, tubulointerstitial lesions, mesangial expansions, and atherosclerosis | Inhibiting AGES formation and sorbitol levels in kidney [27] |
|        |                                                                        | Type 1 diabetic animal study (WBN/Kob rats)   | Preventing diabetic kidney damage                                                                                                      | Reducing renal oxidative injury and expression of FN/TGF-β1 proteins [28, 29] |
| HLBW   | Trigonella foenum-graecum L. (TFG) and Psoralea corylifolia L. (PC)     | Type 2 diabetic animal study (HFD + STZ induced rats) | Improving hyperglycemia, hyperlipidemia, and proteinuria Through attenuating renal oxidative stress via PKC-α/NADPH oxidative pathway [31] |                                                                                            |
| LDP    | Rehmannia glutinosa, Cornel (manufactured), Moutan cortex, Yam, Poria cocos, and Alisma | Human study (DN patients)                     | Improving symptoms and signs of DN, inhibiting EAR activity, lowering UAER levels, β₂-microglobulin in blood, and urine, and relieving DN | [32, 33]                                                                 |
| Name           | Origins                                                                 | Methods                              | Results                                                                                                                                  | Pathways                                                                                           |
|---------------|--------------------------------------------------------------------------|--------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------|
| Oryeongsan    | Poria, Alismatis rhizoma, Polyporus umbellatus (Pers.) Fries, rhizoma Atractylodis macrocephala, and Ramulus Cinnamomi Cassiae | *Type 1 diabetic animal study (STZ induced rats)* | Decreasing plasma glucose, UAER, and Ccr, attenuating mesangial matrix expansion, and downregulating increased NF-κB, TGF-β1 expression, elevated AGEs, and FN accumulation | Through attenuating increased NF-κB and TGF-β1 expression [34]                                      |
|               |                                                                          | *Type 2 diabetic animal study (db/db mice)* | Decreasing TC and TG, improving blood glucose, insulin, glucose tolerance, and HOMA-IR, Ccr, urine albumin, and BUN, and reducing TGF-β1, Smad2/4, collagen IV, CTGF, and TIMP | Through disturbing the TGF-β1/Smad3 pathway [35]                                                  |
| QJC           | Radix astragali, Hirudo, Rehmannia root, and rhizoma Polygonati           | *Human study (DN patients)*           | Decreasing SBF and DBS, increasing ALB, and slowing down the increase of Scr and decrease of eGFR | [36]                                                                                               |
| QWG           | Radix astragali, radix Rehmanniae, Euonymus alatus, and Rhubarb           | *Type 2 diabetic animal study (KK-Ay mice)* | Alleviate renal pathological changes and decreasing TGF-β1 expression                  | Through inhibiting TGF-β1 expression [37]                                                           |
| SKW           | Radix astragali, Herba Leonuri                                           | *Type 1 diabetic animal study (STZ induced rats)* | Protecting renal function                                                                                                               | Through increasing NO and decreasing TGF-β1 expression; affecting podocytes special proteins expression [38] |
|               |                                                                          | *Type 1 diabetic animal study (STZ induced rats)* | Alleviating morphological damage of kidney Suppressing FN secretion                                                                 | Through reducing Ang II in plasma and kidney and inhibiting renal AT(1)R [39] Through TGF-β1 way [38] |
|               |                                                                          | *Cellular study (mesangial cells)*     |                                                                                                                                        |                                                                                                    |
| SQABC         | Radix astragali and Salvia miltiorrhiza                                  | *Type 1 diabetic animal study (STZ induced rats)* | Reducing 24 h UP excretion and improving reabsorption function Protecting HG injured NRK-52E cells and improving protein uptake | Through enhancing antioxidative activity and upregulating megalin [40, 41]                           |
|               |                                                                          | *Cellular study (NRK-52E cells)*       |                                                                                                                                        |                                                                                                    |
| TSF           | Astragalus, raw Rehmannia root, sanchi root, euonymus branchlet, rhubarb, bitter orange, and dogwood fruit | *Human study (DN patients)*           | Regulating and improving phospholipids metabolism Decreasing in vivo Cys, Hcy, SAM, and SAH Upreregulating JAK1, JAK2, and STAT3 and downregulating STAT4 | Through inhibiting PKC pathway and reducing phospholipids metabolism; improving in vivo hypomethylation and oxidative stress [42, 43] Regulating the JAK/STAT/SOCS pathway [44] |
|               |                                                                          | *Type 2 diabetic animal study (db/db mice)* |                                                                                                                                        |                                                                                                    |
| TSL           | Radix astragali, radix Rehmannia, leech, bile south star, Artemisia anomala, and Ze lan | *Type 1 diabetic animal study (STZ + nephrectomized rat)* | Decreasing ECM components                                                                                                               | Through downregulating TGF-β1 and TIMP-2 and upregulating MMP-2 expression [45]                      |
| Name       | Origins                                                                                      | Methods                                                                 | Results                                                                                                                                                                                                 |
|------------|---------------------------------------------------------------------------------------------|-------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| TXL        | Scorpion, leech, Centipede, groundbeetle, Borneol, radix peonies, and ginseng             | Human study (DN patients)                                               | Improving renal function, repairing the renal tubular interstitial damage, and delaying the progression of DN through reducing plasma ET-1 and UAER [46]                                                   |
|            |                                                                                             | Cellular study (HKCs)                                                   | Lowering miRNA-21 expression in tissue, serum, and cells, increasing E-cadherin and decreasing α-SMA expression, and decreasing collagen IV and FN and increasing Ccr through regulating miRNA-21-induced EMT [47] |
|            |                                                                                             | Type 2 diabetic animal study (KK-Ay mice)                              | Decreasing TGF-β1 and Smad 3 expressions, restoring Smad 7, decreasing collagen IV, FN, and 24 h UAER, BUN, and increasing Ccr through inhibiting glucose and lipid metabolism and enhancing myocardial metabolism [54] |
| XCHT       | Radix paeoniae rubra, and ginseng                                                           | Human study (DN patients)                                               | Improving renal function, repairing the renal tubular interstitial damage, and delaying the progression of DN through reducing plasma ET-1 and UAER [46]                                                   |
|            |                                                                                             | Type 2 diabetic animal study (KK-Ay mice)                              | Decreasing the expression of TGF-β1, FN, and collagen IV and increasing BMP-7 through decreasing oxidative stress and production of TGF-β1, FN, and collagen IV [48]                                     |
| XKG        | Radi et rhizoma, rhizoma, cortex, and radix Scutellariae                                   | Human study (DN patients)                                               | Improving HbA1c and FBG, TC, TG, UAER, Scr, ANP, ET-1, and VEGF through modifying ANP, ET-1, and VEGF [56]                                                                                               |
| XZT        | Rhizoma aconitum, cortex, and radix Scutellariae                                           | Human study (DN patients)                                               | Improving HbA1c and FBG, TC, TG, UAER, Scr, ANP, ET-1, and VEGF through modifying ANP, ET-1, and VEGF [56]                                                                                               |
| ZDP        | Salsola herbal, rhizoma et rhizoma, and radix Scutellariae                                 | Human study (DN patients)                                               | Improving HbA1c and FBG, TC, TG, UAER, Scr, ANP, ET-1, and VEGF through modifying ANP, ET-1, and VEGF [56]                                                                                               |
| ZQR        | Fritillariae candida, Polygonum multiflorum, and radix Scutellariae                          | Human study (DN patients)                                               | Improving HbA1c and FBG, TC, TG, UAER, Scr, ANP, ET-1, and VEGF through modifying ANP, ET-1, and VEGF [56]                                                                                               |
2.1.9. Liuwei Dihuang Pill (LDP). Liuwei Dihuang Pill (LDP), one formulation in the ancient Chinese medicine, includes six crude drugs: *Rehmannia glutinosa*, fructus corni, cortex *Mountain, Dioscorea opposita*, *Poria cocos*, and *Alisma*. A previous study in DN patients showed that LDP could improve symptoms and signs of DN and inhibit erythrocyte aldose reductase (EAR) activity and lower UAER levels, improve symptoms and signs of DN and inhibit erythrocyte aldose reductase (EAR) activity and lower UAER levels, improve symptoms and signs of DN and inhibit erythrocyte aldose reductase (EAR) activity and lower UAER levels.

2.1.10. Oryeongsan (Wulingsan). Oryeongsan (Wulingsan), also named as Hoelen Five Herb Formula, is composed of five crude drugs: *Poria*, *Alismatis rhizoma*, *Polyporus umbellatus* (Pers.) *Fries*, rhizoma *Atractylodis macrocephala*, and *Ramulus Cinnamomi Cassiae*. A previous study showed that Oryeongsan could play renal protective roles in lowering plasma glucose and ameliorating glycation-mediated renal damage through attenuating increased NF-κB and TGF-β1 expression in STZ induced diabetic rats [34]. Further study showed that Oryeongsan could ameliorate insulin resistance and DN in db/db mice by disturbing the TGF-β1/Smad3 pathway [35].

2.1.11. Qizhi Jiangtang Capsule (QJC). Qizhi Jiangtang Capsule (QJC) is composed of four crude drugs: radix astragali, *Hirudo*, *Rehmannia* root, and rhizoma *Polygonati*. In a multicenter randomized clinical study, QJC has been shown to reduce urinary protein effectively and delay the progression of renal function in treating 3b DN patients [36].

2.1.12. Qiwei Granule (QWG). Qiwei Granule (QWG) is composed of radix astragali, radix *Rehmannia*, *Euonymus alatus*, and *Rhubarb*. QWG could alleviate renal pathological changes and decrease TGF-β1 expression in the type 2 diabetic KK-Ay mice, which suggested that QWG could play roles in preventing and curing DN [37].

2.1.13. Shenkangwan (SKW). Shenkangwan (SKW) is composed of two crude drugs: *radix astragali* and *Herba Leonuri*. SKW was reported to protect renal function by increasing NO production and decreasing TGF-β1 excretion in the mesangial cells from diabetic rats [38]; in diabetic rats SKW could reduce FN expression in kidney [59] while in rat mesangial cells SKW has been shown to suppress FN secretion via TGF-β1 signal way [60]. Another study showed that in STZ induced diabetic rats SKW could protect renal function and alleviate the functional and structural damage of podocytes possibly by reducing desmin and increasing podocin expression [61], and SKW could offer renal protection against DN by reducing Ang II levels in the plasma and kidney tissues and inhibiting renal AT(1)R expressions [39]. All the data supply precise mechanism of SKW treating DN.

2.1.14. Supplementing Qi and Activating Blood Circulation (SQABC). Supplementing Qi and activating blood circulation (SQABC) is composed of radix astragali and *Salvia miltiorrhiza* and has been shown to reduce 24 h urinary protein excretion and improve tubular reabsorption function by enhancing renal tissue activity of antioxidant and upregulating melanin expression in tubular epithelial cells in STZ induced diabetic rats [40]. Another in vitro study showed that supplementing Qi and activating blood circulation could protect HG injured NRK-52E cells and improve protein uptake by increasing melanin expression [41].

2.1.15. Tangshen Formula (TSF). Tangshen Formula (TSF) is composed of *Astragalus, raw Rehmannia* root, sanchi root, *Euonymus* branchlet, *rhubarb*, bitter orange, and dogwood fruit. TSF has been shown to regulate and improve phospholipids metabolism in DN patients related with inhibition of PKC pathway and the corresponding reduction of phospholipase A2 activity [42]. In a study on the Hcy metabolism of DN patients, TSF could improve in vivo hypomethylation and oxidative stress showing similar favorable effect to western medicine in the treatment of DN [43]. In the molecular mechanism study using a db/db mice model, TSF showed beneficial effects on DN treatment via regulating the JAK/STAT/SCOS signaling pathway [44].

2.1.16. Tongshenluo (TSL) Capsule. Tongshenluo (TSL) capsule is composed of six crude drugs: radix astragali, radix *Rehmannia*, *leech*, bile south star, *Artemisia annulata*, and *Ze lan*. TSL has been shown to decrease the levels of FBG, HbA1c, and urinary mAlb in the subtotal nephrectomy plus STZ induced diabetic rats and decrease the components of ECM through downregulating TGF-β1 and TIMP-2 and upregulating MMP-2 expression [45].

2.1.17. Tongxinluo (TXL). Tongxinluo (TXL) capsule include 8 crude drugs: scorpion, leech, *centipede*, *ground beetle*, *cicada*, *borneol*, radix *Paoniae rubra*, and *ginseng*. TXL capsule has been shown to improve renal function, repair the renal tubular interstitial damage, and delay the progression of DN patients by reducing plasma ET-1 and UAER [46]. TXL was also demonstrated to ameliorate renal function and structure by regulating miRNA-21-induced EMT, suggesting miRNA-21 may be one of the therapeutic targets for TXLC in DN [47]. Another study showed that TXL could also successfully inhibit TGF-β1 induced EMT in DN [62].

2.1.18. Xiao Chai Hu Tang (XCHT). Xiao Chai Hu Tang (XCHT, Shosaiko-to in Japanese) is a herbal drug formula extensively applied in TCM and Japanese Kampo medicine, comprising seven medicinal plants: radix bupleuri, *Scutellaria baicalensis* Georgi radix, *Panax ginseng*, *Pinellia ternata* tuber, *Glycyrrhiza glabra*, ginger slice, and *Zizyphus vulgaris* Lam. *fructus*. XCHT has been shown to decrease the expression of TGF-β1, FN, and collagen IV accompanied with increased BMP-7 expression in STZ induced diabetic
mice and HG stimulated RMC, which was mediated through decreasing oxidative stress and productions of TGF-β1, FN, and collagen IV in renal cortex during the development of DN [48].

2.1.19. Xiaoake Granule (XKG). Xiaoake granule (XKG, Xiaoake Keli in Chinese) includes four crude drugs: radix astragali, Mountain Cornus, leech, and winged euonymus twig. It was reported that XKG could decrease fasting blood pressure and 24 h urinary protein excretion in the 3/4 nephrectomy and STZ induced diabetic rats groups [49]. In the subsequent mechanism study, XKG was proved to exert renal protective effect in DN through downregulating TGF-β1 expression in rat mesangial cells [50].

2.1.20. Xiexin Decoction (XXD). Xiexin decoction (XXD) is composed of three crude drugs including radix et rhizoma rhizoma, rhizoma coptidis, and radix Scutellaria and has been used for the treatment of DM for at least 1700 years. One study in HFD-fed plus STZ induced rats showed that XXD could attenuate albuminuria and renal pathological changes, reduce AGEs, inhibit RAGE and inflammation factors expression, suppress NF-κB, and downregulate renal TGF-β1. All these data suggested that renal protective potential of XXD was involved in inhibition of inflammation through downregulating NF-κB pathway, reducing renal AGEs and RAGE in diabetic rats [51]. A recent study of XXD components in db/db mice showed that multicomponent herbal therapeutic formulations could be a useful approach for the treatment of DN through reducing the expression of NF-κB and TGF-β1 [52].

2.1.21. Xianzhen Tablet (XZT). Xianzhen tablet (XZT, a Chinese patent compound recipe), is composed of astragalus radix, radix Rehmannia, fructus ligustri lucidi, Scutellaria baicalensis Georgi, rhizoma coptidis, dodder weed, fairy spleen, and Salvia miltiorrhiza. XZT was reported to decrease blood glucose and HbA1c in diabetic rats, improve renal function, ameliorate proteinuria, and reduce glomerular extracellular matrix expansion and thickness of basement membrane, which was mediated by the inhibition of AGES accumulation and RAGE mRNA levels in the kidney cortex of STZ induced diabetic rats [53].

2.1.22. Zhibai Dihuang Pill (ZDP). Zhibai Dihuang Pill (ZDP) is one of the TCM preparations, composed of a extract of Astragalus membranaceus, cortex phellodendri, radix Rehmannia preparata, rhizoma Dioscorea, fructus corni, cortex Moutan, rhizoma Alismatis, and Poria. ZDP has been revealed to have protective effects in experimental DN animal models and DN patients. In a recent metabolomic analysis of ZDP in the treatment of STZ-induced diabetic rats, ZDP could ameliorate DN by intervening in some dominant metabolic pathways such as inhibiting glucose and lipid metabolism and enhancing methyamine metabolism [54].

2.1.23. Zao Huang Mixture (ZHM). Zao Huang Mixture (ZHM) is composed of extracts of Sargassum and rhizoma rhizi. One study has shown that ZHM could prevent the process of DN by decreasing the expression of TGF-β1 and type IV collagen in HG stimulated human glomerular mesangial cells [55].

2.1.24. Zhenqing Recipe (ZQR). Zhenqing Recipe (ZQR), a Chinese herbal prescription composed of 3 crude drugs: fructus ligustri lucidi, Eclipta prostrata, and Dioscorea opposita, has been used to improve renal function of DN patients. It is a TCM for treating DN and relevant underlying mechanism [112]. Astragaloside IV (ASI) in radix astragali is considered to be an active constituent; ASI could inhibit human tubular epithelial cells apoptosis and reduce TGF-β1 expression, suggesting a new approach to the treatment of DN [113].

2.1.25. Zishentongluo (ZSTL). Zishentongluo (ZSTL) is composed of eleven Chinese herbs: raw Astragalus, Angelica, safflower, zedoary turmeric, Dodder, radix Rehmannia, dogwood, Poria, Epimedium, earthworm, and Schisandra. ZSTL has been shown to be superior to benazepril in improving the metabolic and renal function in DN patients at early stage partially by modifying ANP, VEGF, and ET-1 expressions [56].
| Name             | Origins                                                                 | Methods                                      | Results                                                                                     | Pathways                                               |
|------------------|-------------------------------------------------------------------------|----------------------------------------------|--------------------------------------------------------------------------------------------|-------------------------------------------------------|
| Astragalus       | Radix astragali                                                        | *Human study* (DN patients)                  | Decreasing BUN, Scr, and proteinuria and improving Ccr and serum albumin level               | Rebalancing TGFβ/Smads signaling                      |
|                  |                                                                         | *Type 2 diabetic animal study* (KK-Ay mice) | Increasing Smad7 expression, inhibiting TGFβR-1, Smad3, and its phosphorylation expression, and decreasing TGF-β1 mRNA level |                                                       |
|                  |                                                                         | *Cellular study* (kidney fibroblast)         | Upregulating c-met expression                                                              | c-met pathway [65]                                    |
| BBR              | *Coptis chinensis, Hydrastis Canadensis, Berberis aristata, Berberis aquifolium, and Arcangelisia flava* | *Type 2 diabetic animal study* (HFD + STZ induced rats) | Suppressing histological and ultrastructural changes in kidney, improving glucose and lipid metabolism disorder, increasing cAMP, downregulating GRK2 and GRK3, and upregulating GRK6 | Modulating the expression of GRKs in G protein-AC-cAMP signaling pathway [66] |
| Curcumin         | *Carcum longa L. (CLL)*                                                 | *Type 2 diabetic animal study* (db/db mice)  | Decreasing albuminuria and attenuating glomerular sclerosis                                | Inhibiting phosphorylation of STAT3 and degradation of IκB [67] |
|                  |                                                                         | *Cellular study* (mesangial cells)           | Decreasing hyperglycemia, renal AGE formation, RAGE, Scr, Ccr, and NF-κB, TGF-β1 and enhancing reduced SOD activities | Reducing AGEs-induced ROS [68]                        |
| DMDD             | Tuberous roots of *A. carambola L.*                                    | *Type 2 diabetic animal study* (KK-Ay mice)  | Decreasing hyperglycemia, renal AGE formation, RAGE, Scr, Ccr, and NF-κB, TGF-β1 and enhancing reduced SOD activities | Decreasing AGES and TGF-β1 levels [69]               |
| DP               | Dragon’s blood                                                          | *Cellular study* (human mesangial cells)     | Preventing renal fibrosis                                                                  | Inhibiting SGKI and FN expression [70]                |
| EGB              | *Ginkgo biloba leaves*                                                  | *Human study* (DN patients)                  | Decreasing urinary mALB, α1-MG, IgG, TGF, RBP, and NAG                                    | Through decreasing sICAM-1 and sVCAM-1 [71, 72]       |
|                  |                                                                         | *Cellular study* (mesangial cells)           | Suppressing MC hypertrophy and ECM accumulation                                             | Through TGF-β1 and Smads pathway [73]                 |
| FA               | Seeds and leaves of plants                                              | *Type 1 diabetic animal study* (OLETF rats)  | Decreasing blood glucose and urinary ACR, mesangial matrix expansion, and glomerular basement thickness | Through reducing oxidative stress and inflammation [74, 75] |
| Flos A. manihot  |                                                                         | *Type 1 diabetic animal study* (STZ induced rats) | Preventing renal damage and podocyte apoptosis                                              |                                                       |
| Genipin          | *Gardenia jasminoides*                                                 | *Type 1 diabetic animal study* (STZ induced mice) | Ameliorating body weight loss and urine albumin leakage, attenuating GBM thickness, suppressing upregulation of UCP2, and restoring podocin and WT1 expression | Through suppressing upregulation of mitochondrial UCP2 [77] |
| HCT              | *Houttuynia Cordata Thunb.*                                            | *Type 1 diabetic animal study* (STZ induced rats) | Reducing UAER, Ccr, TGF-β1, and collagen I and increasing BMP-7                            | Decreasing TGF-β1 and increasing BMP-7 [78]           |
| Icarin           | Herba epimedii                                                         | *Type 1 diabetic animal study* (STZ induced rats) | Relieving renal damage                                                                    | Inhibiting TGF-β1 and Coll IV expression [79]         |
| LAB              | *Salvia miltiorrhiza*                                                  | *Type 1 diabetic animal study* (STZ induced rats) | Renal MDA, microalbuminuria, mesangial expansion, and glomerular hypertrophy, TGF-β1 and fibronectin secretion, and PKC and ROS | TGF-β1 pathway [80]                                  |
|                  |                                                                         | *Cellular study* (mesangial cells)           | Inhibiting VSMCs proliferation and migration                                               | PKC and ROS pathway [80]                             |
|                  |                                                                         | *Cellular study* (VSMCs)                     |                                                                                           | Nrf2-ARE-NQO1 [81]                                    |
| Name                  | Origins | Methods                                      | Results                                                                                                                                 |
|-----------------------|---------|----------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------|
| LBP                   | Fruit of goji berry | Type 1 diabetic animal study (STZ-induced rats) | Increasing antioxidant enzymes and increasing scavening oxygen radicals, decreasing hyperglycemic, NF-κB, capase-3, capase-8, capase-9, and Bax expression, alleviating glomerular hypertrophy and ECM accumulation [83] |
| LGP                   | Averrhoa carambola L. (Oxalidaceae) root     | Type 1 diabetic animal study (STZ-induced mice) | Decreasing SOD, GSH-PX, and CAT, reducing MDA, decreasing blood glucose, Scr, Cr, and urine protein and downregulating TGF-β1, MCP-1, IL-6, ICAM-1, and RAGE through attenuating oxidative stress and ameliorating inflammation [88–90] |
| MC                    | Moutan cortex | Human study (DN patients)                     | Decreasing hyperglycemia, NF-κB, caspase-3, caspase-8, caspase-9, and Bax expression; alleviating glomerular hypertrophy and ECM accumulation | [83] |
| Moronoside            | Corni Fructus                          | Type 1 diabetic animal study (STZ-induced rats) | Decreasing FBG, Ccr, 24h urine protein, and serum Cr; increasing SOD, GSH-PX, and CAT; decreasing MDA and ROS levels; and inhibiting NF-κBp65 and MCP-1 expression through regulating oxidative stress and inflammation [97] |
| PNS                   | R. rosea (Radix notoginseng)             | Type 1 diabetic animal study (STZ-induced rats) | Decreasing FBG, Ccr, and 24h urine protein; increasing SOD activity and total antioxidant capacity; decreasing MDA and ROS levels; and inhibiting NF-κBp65 and MCP-1 expression through decreasing TGF-β1 expression [96] |
| Puerarin              | Pueraria lobata (Radix puerariae)         | Type 1 diabetic animal study (STZ-induced rats) | Decreasing hyperglycemia, NF-κB, caspase-3, and Bax expression; alleviating glomerular hypertrophy and ECM accumulation | [84] |
| Rhein                 | Rubus chamaemorus (Rubus chinensis)       | Type 1 diabetic animal study (STZ-induced rats) | Decreasing hyperglycemia, NF-κB, caspase-3, and Bax expression; alleviating glomerular hypertrophy and ECM accumulation | [84] |
| Sequoital             | Angelicasinensis, Lignosticum chuangxiong, Cimicifuga heracleifolia, and other plants| Human study (DN patients)                     | Decreasing hyperglycemia, NF-κB, caspase-3, and Bax expression; alleviating glomerular hypertrophy and ECM accumulation | [84] |
| SF                    | Rosmarinus officinalis, Lepidium thlaspi, Lepidium sativum, and other plants | Type 2 diabetic animal study (HFD-STZ-induced rats) | Decreasing hyperglycemia, NF-κB, caspase-3, and Bax expression; alleviating glomerular hypertrophy and ECM accumulation | [84] |
| Name       | Origins                        | Methods                                      | Results                                                                                           | Pathways                                                                                   |
|------------|--------------------------------|----------------------------------------------|---------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|
| Skimmin    | Hydrangea paniculata           | Type 1 diabetic animal study (STZ induced rats) | Decreasing Scr and blood glucose level, alleviating glomerular segmental sclerosis and tubular vacular degeneration, and downregulating TGF-β1 and TGF-β1 receptor I expression | Through inhibiting TGF-β1 pathway [100]                                                   |
| SM         | Salvia miltiorrhiza            | Type 1 diabetic animal study (STZ induced rats) | Decreasing TGF-β1, CTGF, PAI-1, FN ED-1, collagen IV, and RAGE overexpression and protecting tubular function and structure | Through inhibiting TGF-β1 pathway, oxidative stress, and inflammation [101–103]             |
| TGP        | Paeonia lactiflora Pall.       | Type 1 diabetic animal study (STZ induced rats) | Elevating antioxidant enzyme and decreasing p-p38 MAPK and NF-κB Decreasing Scr, BUN, and 24 h UP and improving renal histopathology | Through inhibiting oxidative stress [104]                                                  |
|            |                                | Type 2 diabetic animal study (HFD + STZ induced rats) |                                                                                                    | Through inhibiting Wnt/beta-catenin signaling pathway [105]                                  |
| TMP        | Ligusticum chuanxiong          | Type 1 diabetic animal study (STZ induced rats) | Improving renal function                                                                            | Through downregulating VEGF expression [106]                                               |
| Triptolide  | Diterpene purified from TwHF   | Type 2 diabetic animal study (db/db mice)     | Decreasing albuminuria, alleviating glomerular hypertrophy and podocyte injury, and attenuating inflammation and oxidative stress in kidney | Through inhibiting inflammation and dyslipidemia [107]                                      |
| TwHF       |                                | Human study (DN patients)                     | Preventing podocyte injury                                                                        | Downregulating TGF-β1, OPN, and CTGF [108]                                                |
| VOMBP      | Magnolia biondii Pamp.         | Type 1 diabetic animal study (STZ induced rats) | Decreasing 24 UmAlb, sP-selectin in serum, and P-selectin in renal tissue                           | Inhibiting P-selectin [109]                                                                |
treatment for DN probably mediated by the inhibition of p38 MAPK pathway activation and HGF overproduction [113].

2.2.2. Berberine (BBR). Berberine (BBR), an effective compound of herbal TCM, includes Coptis chinensis, Hydrastis Canadensis, Berberis aristata, Berberis aquifolium, and Arcangelia flava.

BBR treatment could restore renal functional parameters, improve glucose and lipid metabolism disorders, suppress alterations of histological and ultrastructural changes in kidney, and increase cAMP levels in HFD-fed plus STZ induced diabetic rats, and the renal protective effect is exerted by modulating the G protein-coupled receptor kinases (GRKs) in G protein-AC-cAMP signaling pathway [66]. A previous study showed that BBR-containing TCM could increase glucose uptake and lipid oxidation with insulin sensitivity in Zucker diabetic fatty rats [16].

2.2.3. CLL/Curcumin. Curcuma longa L. (CLL) has been widely used to prevent diabetic vascular complications in recent years. Curcumin and demethoxycurcumin are isolated from CLL and have been shown to potentially protect DN by reducing AGE-induced oxidative stress and restoring AGE-induced mesangial cell apoptosis [68]. In the treatment of DN in db/db mice, curcumin has been shown to decrease albuminuria and attenuate glomerular sclerosis by inhibiting phosphorylation of STAT3 and degradation of IκB [67]. A systemic review and meta-analysis of fourteen randomized controlled trials suggested that curcumin has protective potentials on the kidneys of diabetic rats/mice [114].

2.2.4. 2-Dodecyl-6-methoxycyclohexa-2,5-diene-1,4-dione (DMDD). 2-Dodecyl-6-methoxycyclohexa-2,5-diene-1,4-dione (DMDD), isolated from the tuberous roots of A. carambola L. (Oxalidaceae), has been shown to enhance the reduced SOD activities in the kidney of KK-Ay mice and inhibit the progression of DN through decreasing AGES and TGF-β1 levels [69].

2.2.5. Dracorhodin Perchlorate (DP). Dracorhodin perchlorate (DP), one of the main compositions of Dragon’s blood, has been shown to prevent and retard renal fibrosis of DN partially through inhibiting SGK1 and FN expression in human mesangial cells [70].

2.2.6. EGB. Ginkgo biloba extract (EGB), taken from the leaves of Ginkgo biloba, is a mixture containing flavonoid glycosides and has been proven to ameliorate hemodynamics, suppress PAF and ACE activities, scavenge ROS, relax vascular smooth muscles, and suppress AGES expression. In a previous study on DN patients, EGB treatment has been shown to decrease urinary mALB, α1-MG, IgG, TF, RBP, and NAG in DN patients compared with control group, which suggested that EGB has renoprotective effect on the early DN [71]. The subsequent mechanism study showed that EGB could suppress rat mesangial cells hypertrophy and ECM accumulation through decreasing Smad2/3 and TGF-β1 and increasing Smad7 [73], while in DN patients EGB has been proven to retard early DN development through decreasing serum sICAM-1 and sVCAM-1 levels [72].

2.2.7. Flos Abelsomachus manihot. Flos Abelmoschus manihot (Huangshukuihua in Chinese) has been widely used as the neuroprotective drug for cerebral ischemic reperfusion injury. Total flavone glycosides of flos A. manihot (TFA) contain 7 identified flavone glycosides. TFA pretreatment has been shown to prevent renal damage and podocyte apoptosis in STZ induced rats [76]. A meta-analysis of 27 randomized controlled trials showed that flos Abelmoschus manihot had significant effect on renal function in the treatment of DN deserving further investigation [115].

2.2.8. Genipin. Genipin is a glycone derived from geniposide present in fruit of Généría jasminoides. Genipin has been proven to ameliorate body weight loss and urine albumin leakage, attenuate GBM thickness, and restore the podocyte expression of podocin and WT1 in diabetic mice; the protective effect of Genipin on DN is probably through suppressing the upregulation of mitochondrial UCP2 in STZ induced diabetic mice kidneys [77].

2.2.9. Houttuynia cordata Thunb. (HCT). Houttuynia cordata Thunb. (HCT, Yu Xing Cao in Chinese), pungent in taste and cool in nature, has been reported to reduce urinary proteins in the patients with nephrotic syndrome; HCT has also been shown to protect diabetic kidney function through decreasing the expression of TGF-β1 and increasing the expression of BMP-7 [78].

2.2.10. Icariin. Icariin is a major constituent of flavonoid extracted from the plant herba epimedii and has been shown to relieve renal damage in STZ induced diabetic rats through inhibiting the expression of TGF-β1 and collagen IV protein [79].

2.2.11. LAB. Lithospermate B (LAB), a tetramer of caffeic acid isolated from Salvia miltiorrhiza radix, was identified as antioxidant and PKC inhibitor in the renoprotective effects under diabetic conditions in vivo and in vitro [80]. In the STZ induced diabetic rats, delayed LAB treatment could inhibit renal MDA, microalbuminuria, mesangial expansion, and glomerular hypertrophy, and in mesangial cells LAB could inhibit HG and H2O2 induced TGF-β1 and FN secretion, HG induced intracellular PKC activation, and ROS generation, which suggested that LAB could significantly suppress the progression of diabetic renal injury. A recent study showed that LAB could prevent diabetic atherosclerosis by induction of the Nrf2-ARE-NQO1 pathway to inhibit VSMCs proliferation and migration and vascular damage [81]. All these findings suggested that LAB could be a new therapeutic agent in the treatment of DN. In the subsequent study, Salvia miltiorrhiza could protect STZ induced diabetic rats by inhibiting the overexpression of TGF-β1, CTGF, PAI-1, and FN in renal cortex.

2.2.12. LBP. Lycium barbarum polysaccharide (LBP) is extracted from the fruit of goji berry(Solanaceae); LBP4
has been shown to protect STZ induced diabetic kidney function via decreasing the activation of ERK1/2 through the involvement of PKC in mesangial cells [82].

2.2.13. LGP. Lyoniresinol 3 alpha-O-beta-D-gluco pyranoside (LGP) is isolated from *Averrhoa carambola* L. (Oxalidaceae) root (ACLR), including two chiral lignin glucosides: LGP1 and LGP2. LGP1 treatment has been shown to decrease hyperglycemia and the expression of related proteins including NF-κB, caspase-3, caspase-8, caspase-9, and Bax in STZ induced diabetic mice. LGP1 also could alleviate glomerular hypertrophy, excessive ECM accumulation, and glomerular and tubular basement membrane thickness. All these data suggested that LGP1 could be a potential therapeutic agent in DN [83].

2.2.14. Ligustrazine. Ligustrazine, a bioactive component of Chuangxiong, has been widely used in the treatment of vascular diseases such as myocardial and cerebral infarction in China. A meta-analysis of 25 studies showed that Ligustrazine has therapeutic effect to improve renal function and reduce urine protein excretion in DN patients [84]. Further studies should be conducted to reveal the underlying mechanism for the treatment on DN.

2.2.15. MC. Moutan cortex (MC), the root bark of *Paeonia suffruticosa*, has been shown to have the protective effect against atherosclerosis and inflammation and inhibitory effect on the production of ROS. MC was reported to increase activity of SOD, GSH-PX, and CAT and reduce MDA in vitro or in vivo; furthermore, MC could decrease blood glucose, Scr, and urine protein in HFD-fed plus STZ induced diabetic rats, which suggested that MC has renal protective effect in AGES-induced mesangial cell dysfunction through attenuating oxidative stress pathway [85], while, in AGES-induced rat mesangial cells, MC could inhibit FN and collagen IV expression in matrix [86]. Apart from the abovementioned evidence of renal protective effect on DN, MC could ameliorate activity on the inflammation via target of RAGE in vitro or in vivo [87].

2.2.16. Morroniside. Corni fructus, a constituent of HJG, used as a traditional medicine in China and Japan, has been shown to be superior to aminoguanidine treatment in suppressing hyperglycemia, proteinuria, renal AGE formation, and TGF-β1 expression in STZ induced diabetic rats [116]. Morroniside, isolated from corni fructus, could exhibit protective effects against STZ induced renal damage by inhibiting hyperglycemia and oxidative stress [88]. Another study showed that components of corni fructus could play protective effect on early stage of DN in type 2 diabetic rats mediated by the regulation of podocytes. Loganin from corni fructus and its derivatives could inhibit the expression of FN and IL-6 in the HG stimulated mesangial cells, which supported the traditional use of corni fructus in DN and relevant kidney diseases [117].

2.2.17. Panax Notoginoside (PNS). Panax notoginoside (PNS) is extracted from radix notoginseng and has been shown to protect kidney in type 1 diabetic rats at early stage through inhibiting the expression of VEGF protein and enhancing BMP-7 expression in the kidney [89]. Another report showed that the protective effect of PNS in kidney was mediated by inhibiting TGF-β1 expression and enhancing the expression of Smad7 [90]. Ginsenoside Rg1, an active ingredient isolated from PNS, has been shown to improve the renal pathological changes in STZ induced diabetic rats through reducing TGF-β1 expression and inflammatory reaction factors including CRP and TNF-α [118]. Ginsenoside Rgl also could effectively relieve aldosterone-induced oxidative stress through which it indirectly inhibits aldosterone-induced podocyte autophagy [119].

2.2.18. Puerarin. Puerarin, 7-hydroxy-3-(4-hydroxyphenyl)-1-benzopyran-4-one-8-b-D-glucopyranoside-6, is one of the major isoflavonoid compounds from the root of *Pueraria candollei* wall of Leguminosae family. A previous study showed that Puerarin could protect DN rats by inhibiting collagen IV expression [91]; further study in STZ induced diabetic rats showed that Puerarin could protect kidney function through downregulating MMP-9 and attenuating eNOS expression [92, 93].

2.2.19. Rehmannia Radix (Di Huang). Rehmannia radix (Di Huang) was mostly mentioned and investigated; it has been proven to reduce hyperglycemia, ameliorate renal dysfunction, prevent senility, and improve hemorheology. In a previous experimental study *Rehmannia* radix has been shown to inhibit the progression of DN [120]. Catalpol is an iridoid glucoside compound mainly present in *Rehmannia* radix and other plants and has been shown to reduce ECM accumulation by inhibiting the expression of TGF-β1, CTGF, and Ang II in HFD-fed plus STZ induced diabetic rats [121].

2.2.20. Rhein. Rhein (4,5-dihydroxyanthraquinone-2-carboxylic acid) is purified from rhubarb (*Rheum officinale*). Rhein has shown reduction of UAE faster than simvastatin and decrease of ECM levels along with decreased TGF-β1 and FN immunohistochemistry expression in db/db renal tissue, which was supposed via regulation of dyslipidemia [94]. Another study showed that Rhein could inhibit the hypertrophy of rat renal proximal tubular epithelial cells stimulated by HG and Ang II [95].

2.2.21. Rhodiola rosa. *Rhodiola rosa* (R. rosa) is grown at northern latitudes and high altitudes of the world; *Rhodiola rosa* extract has been used to protect kidney function including reducing FBG, TC, TG, Ccr, and 24h urinary albumin in HFD-fed plus STZ induced diabetic rats through decreasing renal expression of TGF-β1 [96].

2.2.22. Rosa laevigata Michx. (RLM). *Rosa laevigata* Michx. (RLM), a commonly used TCM for the treatment of urinary tract infection and antioxidative treatment, could play a critical role in the pathogenesis of DN through increasing the activity of SOD and total antioxidant capacity, decreasing MDA and ROS levels, and inhibiting NF-κB p65 and MCP-1 expression following increased IkB protein expression in STZ
induced diabetic rats; all the data suggested that RLM could be a therapeutic potential for DN [97].

2.2.23. Sequoyitol. Sequoyitol is a natural compound present in a lot of plants (e.g., Aristolochia arcuata, Amentotaxis yunnanensis, and Crossostephium chinesis); oral and subcutaneous administrations of sequoyitol could ameliorate hyperglycemia and glucose intolerance in ob/ob mice. Sequoyitol has been shown to ameliorate the progression of DN in HFD-fed plus STZ induced rats through glucose-lowering effects, antioxidant activity, and regulation of TGF-β1 expression [98].

2.2.24. SF/FA. Sodium ferulate (SF), extracted from Angelica sinensis, Lignosticum chuangxiong, Cimicifuga heraclefolia, and other plants, has platelet aggregation inhibitory, anti-thrombotic, and antioxidant activities in animals and humans. A preliminary study on DN patients showed that SF could lower UAER level and improve renal function through decreasing endothelin (ET) and inhibiting the combination of ET with its receptor [99]. A meta-analysis of 14 randomized controlled trials involving 906 patients showed that SF is superior in reducing UAER, ET, BUN, Scr, and TC and increasing HDL-c without affecting FBG and TG [122]. Ferulic acid (FA) is a phenolic acid extracted from the seeds of most plants and has antioxidant activities, hypoglycemic and hypolipidemic effects, hypotensive effects, and anti-inflammatory effects. In the FA treated OLETF rats, blood glucose and urinary ACR were decreased significantly; in renal histopathology glomerular basement membrane thickness and mesangial matrix expansion were decreased through reducing oxidative stress and inflammation [74, 75].

2.2.25. Skimmin. Skimmin, a major active component from Hydrangea paniculata, has been reported to decrease Scr and blood glucose level and alleviate glomerular segmental sclerosis and incidence of tubular vacuolar degeneration by downregulating the TGF-β1 and TGF-β1 receptor I expression in STZ induced diabetic rats [100].

2.2.26. SM. Salvia miltiorrhiza (SM, commonly known as Danshen in Chinese) has been shown to have the anti-inflammatory, antioxidative, and organ protective effects. A previous study showed that SM could protect STZ induced diabetic rats from DN by suppressing the overexpression of TGF-β1, CTGF, PAI-1, and FN in renal cortex [101]. Another study showed that SM could ameliorate TGF-β1 levels in serum and kidney and reduce the levels of collagen IV ED-1 and RAGE in the diabetic kidney [102]. Danshen injection, the aqueous extracts of SM, could protect diabetic rats associated with preservation of tubular function and structure from hyperglycemia induced oxidative stress, advanced glycation stress, and megalin expression deletion [103].

2.2.27. TGP. Total glucosides of paeyon (TGP), extracted from the root of Peaonia lactiflora Pall., have been shown to have the therapeutic effect in the experimental DN. TGP treatment in the STZ induced diabetic rats could prevent diabetic renal damage against oxidative stress through decreasing upregulated p-p38 MAPK and NF-κB P65 expressions [104]. And, in the HFD-fed plus STZ induced rats, TGP could improve kidney damage and delay the development of DN by inhibiting Wnt/beta-catenin signaling pathway [105].

2.2.28. TMP. Tetramethylpyrazine (TMP) is isolated from Ligusticum chuanxiong and has been used in the treatment of stroke and cardiovascular diseases. TMP was reported to reduce diabetic kidney damage partially by downregulating the expression of VEGF in the kidney [106].

2.2.29. Triptolide/GTW/TwHF. Triptolide, active diterpene purified from Tripterygium wilfordii Hook. F. (TwHF), has been reported to have anti-inflammatory, antioxidative, immunosuppressive, and podocyte-protective effects. A recent study showed that triptolide could attenuate albuminuria in db/db diabetic mice accompanied with alleviated glomerular hypertrophy and podocyte injury, while inflammation and dyslipidemia were also attenuated [107]. Triptolide is one of the major active components of multiglycoside of TwHF (GTW), and GTW has been applied extensively for the treatment of CKD in China as an anti-inflammatory agent. GTW could prevent glomerular lesion in STZ induced diabetic model through decreasing urine albumin and ameliorating glomerular sclerosis [123]. A recent study showed that TwHF could prevent podocyte injury of DN patients, which may be partly mediated by downregulating the expression of OPN, CTGF, and TGF-β1 [108].

2.2.30. Volatile Oil of Magnolia biondii Pamp. (VOMBP). Volatile oil of Magnolia biondii Pamp. (VOMBP), extracted from herbal TCM Magnolia biondii Pamp., has been reported to protect the kidney in STZ induced diabetic rats by inhibiting the expression of P-selectin in serum and renal tissue [109].

2.3. TCMs Combined Therapy with Western Medicines in DN. Apart from the TCM preparations and single TCM applications in DN, TCMs combined with western medicines have been indicated. Mostly used western medicines were ACEI/ARBs, and combination styles included Tangshen-ling (TSL) with telmisartan [124] in diabetic patients or TSL with benazepril in STZ induced rats [125], triptolide with benazepril in DN patients [126], Bailing Capsule (BC) and benazepril in DN patients [127], and safflower yellow powder injection with benazepril in DN patients [128]. Another report is about Tangshenqing (TSQ) combined with alprostadil in the treatment of DN patients [129]. All data suggested that effects of TCMs combined therapy with western medicines were superior to western medicines treatment alone.

3. Conclusions and Perspectives

Although there are almost no side effects mentioned in numerous scientific reports, a lot of scientific researches indicate that herbal TCM preparations have renal protective
effects on DN according to respective factors, complexity, and variability of TCM preparations still presenting challenges for clinicians seeking scientific evidence to support TCM application in drug discovery. In order to avoid the toxicity and side effects of TCM formulas, there is increasing interest in studying single herbal TCM especially monomers from single herbal TCM on DN. In this review, we found that monomers such as Berberine, curcumin, Ginsenoside Rgl, Pueraian, Rhein, and Ferulic acid have specific protective effect on DN. To translate the therapeutic potentials for DN into reality, placebo-controlled and randomized controlled clinical trials of single herbal TCM and/or monomers from herbal TCM are essential in the future, and prompt meta-analysis is an effective alternative.

Conflict of Interests

The authors have no conflict of interests to declare.

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**Journal of Diabetes Research**

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