Chinese medicines in the treatment of experimental diabetic nephropathy

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Abstract
Diabetic nephropathy (DN) is a severe micro vascular complication accompanying diabetes mellitus that affects millions of people worldwide. End-stage renal disease occurs in nearly half of all DN patients, resulting in large medical costs and lost productivity. The course of DN progression is complicated, and effective and safe therapeutic strategies are desired. While the complex nature of DN renders medicines with a single therapeutic target less efficacious, Chinese medicine, with its holistic view targeting the whole system of the patient, has exhibited efficacy for DN management. This review aims to describe the experimental evidence for Chinese medicines in DN management, with an emphasis on the underlying mechanisms, and to discuss the combined use of herbs and drugs in DN treatment.

Background
Diabetic nephropathy (DN) is a serious micro vascular complication in patients with diabetes mellitus (DM), affecting approximately 40% of patients with type 1 or type 2 DM [1, 2]. It is the predominant cause of chronic kidney disease and renal failure, and is closely associated with many micro vascular diseases, leading to financial and medicinal burdens [3]. Continued hyperglycemia associated with DM is the major cause of kidney dysfunction with metabolic and hemodynamic disorders arising from oxidative stress and inflammation [4].

During DN progression, progressive alterations develop from hyperfiltration through micro albuminuria to macro albuminuria, and finally to renal failure [5]. Renal structural changes are found in the nephrons, especially in the primary part of the glomerulus, including podocyte loss, glomerular basement membrane (GBM) thickening, endothelial cell dysfunction, and mesangial extracellular matrix (ECM) expansion, resulting in protein leakage into the urine [6]. Pulmonary dysfunction [7], hyperlipidemia and non-alcoholic fatty liver disease [8], cardiovascular disease [9], and even heart failure [10] have been reported to be positively associated with DN progression. Therefore, synergistic therapies targeting multiple mediators of DN are required for effective therapeutic strategies [4].

The experimental models used for studying Chinese medicines (CMs) in DN treatment are diverse. For in vivo studies, different doses of streptozotocin (STZ) are administered to mimic type 1 or type 2 DM. Examples of the CMs that have been investigated are Glycyrrhiza uralensis (gan-cao), Carum carvi (zahl-hui-xiang), Allium sativum (da-suan), and Mesona procumbens (xi-an-cao) [11–14]. In addition, alloxan (ALX)-induced mice, db/db mice, KK-Ay mice, and Otsuka Long-Evans Tokushima Fatty (OLETF) rats have been reported for investigation of CMs in DN treatment [15–18]. Meanwhile, glomerular endothelial cells, mouse podocyte cells, renal proximal epithelial cells, murine hepatocytes, mouse mesangial cells, and human mesangial cells are used as in vitro models for anti-DN mechanism studies [19–27]. By applying these models, the majority of studies have reported that CMs such as Acacia nilotica pods (jin-he-huan) [28], Artemisia campestris (huang-ye-hao) [29], Paeonialactiflora (shao-yao) [30], and
Schisandra chinensis (wu-wei-zi) [21, 31] exhibited beneficial effects on all stages of experimental DN and may protect multiple organs. Grapevine leaf (Vitis labrusca) extract was reported to exert hepatoprotective, cardio-protective, and renoprotective effects [32]. Moreover, CM preparations such as Fufang Xueshuantong Capsule (fu-fang-xue-shuan-tong-jiao-nang), Zhengqing Recipe (zheng-qing-fang), and Danggui Buxue Tang demonstrated benefits for DN patients [33–35]. Representative CMs for the treatment of DN at different stages of disease progression and their underlying mechanisms are shown in Fig. 1.

This article aims to review the experimental evidence for the effectiveness of CMs in DN management, with emphasis on their underlying mechanisms, and to discuss the combined use of CM herbs and chemical drugs in DN treatment.

Search strategy and selection criteria
We searched for the terms “traditional Chinese medicine”, “holistic therapy”, and “traditional Chinese medicine prescriptions (or formula)” in combination with “diabetic nephropathy” and “diabetes” in PubMed, Google Scholar, and Web of Science between 1990 and 2014. Manual searches of in-text references from the selected articles were further performed. Studies were included if in vivo models were used to investigate the nephroprotective effects and mechanisms of CMs. Unpublished reports, Letters to the Editor, and the studies that only used in vitro models or did not provide information about the duration of animal studies were excluded.

CMs in experimental DN management

CMs intervention in the early stage of experimental DN

The potential signaling pathways involved in DN pathogenesis regulated by CMs are shown in Fig. 2. The early stage of DN is characterized by hyperfunction and hypertrophy arising from oxidative stress and inflammation [3, 36, 37]. Under chronic hyperglycemia, the extracellular glucose forms advanced glycation end-products (AGEs). Activation of receptor of advanced glycation end-products (RAGE) on the plasma membrane has been proposed to contribute predominantly to the overproduction of reactive oxidative species (ROS) [38].
Meanwhile, the polyol pathway of glucose metabolism activated by the intracellular glucose further aggravates the oxidative stress. Other major sources of excess ROS were reported to be enhanced protein kinase C (PKC) activity caused by activation of the polyol pathway [39] and mitochondrial ROS production in response to mitochondrial damage. As a consequence, nuclear factor (NF)-κB becomes activated, followed by stimulation of pro-inflammatory cytokines (e.g., interleukin [IL]-6), chemokines (e.g., monocyte chemoattractant protein [MCP]-1), adhesion molecules (e.g., intercellular adhesion molecule 1 [ICAM1], vascular cell adhesion protein 1 [VCAM1]), and nuclear receptors (e.g., peroxisome proliferator-activated receptor [PPARs]) [40]. Thereafter, the inflammation induces endoplasmic reticulum (ER) stress via unfolded protein response pathways, resulting in metabolic disorders and apoptosis. Asparagus racemosus (lu-sun), Radix Astragali (huang-qi), Rosa laevigata (jin-ying-zi), and Piper auritum (hu-jiao) were reported to enhance the activities of superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px), leading to attenuation of the oxidative stress [5, 42–44].

**CMs intervention in the incipient stage of experimental DN**

The development of micro albuminuria was reported as an indicator of the incipient stage of DN, arising from endothelial dysfunction [38, 45]. Renal hypertrophy and hyperfiltration induced functional and structural alterations, resulting in micro albuminuria and hypertension, leading to glomerulus sclerosis, and progressing to incipient DN. *Cornus officinalis* (shan-zhu-yu), *Abelmoschus manihot* (huang-shu-kui), *Schisandraceae chinensis* (wu-wei-zi), and *Paeonia lactiflora* (shao-yao) were reported to exhibit anti-micro albuminuria effects, thereby slowing down DN progression [19, 21, 46, 47].
**CMs intervention in the overt and end-stage renal disease (ESRD) stages of experimental DN**

After the incipient stage of DN and under hyperglycemic conditions, mesangial nodules and tubule interstitial fibrosis develop, leading to proteinuria and nephrotic syndrome, and eventually to the overt stage of DN, which is characterized by persistent proteinuria [6]. Without effective control, patients in this stage will deteriorate to ESRD with uremia. As the kidney disease progresses, physical changes in the kidneys often lead to increased blood pressure and cardiovascular disease. In this stage, angiotensin-converting enzyme (ACE) inhibition is the conventional intervention [48]. The goal of treatment is to prevent the progression from micro albuminuria to macro albuminuria, and multiple and more intensive strategies are strongly advised. Avosentan was reported to reduce albuminuria in patients with type 2 DM and overt nephropathy by inhibiting ACE and blocking angiotensin receptors, but can also induce significant fluid overload and congestive heart failure [49]. Averrhoa carambola L. (yam-tao), Salvia miltiorrhiza (dan-shen), and Picrorhiza Rhizoma (hu-huang-lian) can ameliorate DN symptoms safely [50–52]. Representative CMs and their related mechanisms are summarized in Table 1.

Besides targeting the specific molecules involved in DN pathogenesis to exert anti-hyperglycemic and nephroprotective effects, CM has unique characteristics in CN management. In CM, DN is not only a kidney disease, but also an embodiment of the systemic disease in the kidney, which is in accordance with the latest findings for DN pathogenesis [7, 8, 38]. The pathogenesis of DN may be closely related to the dysfunction or impairment of other organs, and therefore treatments for diseases in other organs may be helpful for the amelioration of DN, especially in the overt and ESRD stages. The normal functioning of the human body relies on the coordination of yin and yang, and the five zang organs (wuzang), i.e., the liver (gan), heart (xin), spleen (pi), lung (fei), and kidney (shen), are respectively related to wood (mu), fire (huo), earth (tu), metal (jin), and water (shui) and connected under the laws of inter promotion and interaction (Fig. 3) [53]. Once a significant imbalance occurs, certain symptoms of the kidneys inevitably and predictably arise.

Under hyperglycemic conditions, the oxidative stress and inflammation affect the blood circulatory system, consequently leading to the dysfunction of multiple organs. Cardiovascular disease causes even more deaths than ESRD in patients with DN [38]. The degree of pulmonary function impairment was found to be positively associated with the stage of DN progression [7]. Besides, liver X receptor (LXR) agonists, which are commonly used to treat hyperlipidemia and non-alcoholic fatty liver disease, were shown to ameliorate DN by inhibiting the expressions of osteopontin and other inflammatory mediators in the kidney cortex [8]. Moreover, during DN pathogenesis, glomerular hypertrophy was found to be associated with hyperinsulinemia [54], and has been proposed as a novel therapeutic target for DN [55]. As a systematic micro vascular thrombosis combined with metabolic disorders, DN influences the whole internal environment, and its pathogenesis may be closely related to the dysfunction of other organs.

From this perspective, CM as a therapeutic approach targeting multiple organs is preferred to improve the overall health of DN patients. Experimentally, grapevine (Vitis labrusca L.) leaves exhibited hepatoprotective, cardioprotective, and renoprotective effects in Wistar rats [32]. Besides, extracts from *S. miltiorrhiza* exhibited a regulatory effect on the expression of LXR-α in hyperlipidemic rats [56]. Furthermore, *Liweihuihui Decoction* exhibited a protective effect on early DN in STZ rats [57]. Additionally, a CM prescription, *kangen-karyu*, exhibited hepatoprotective/renoprotective activities through the inhibition of AGE formation and fibrosis-related protein expressions in type 2 diabetes [58]. Yamabe and colleagues systematically conducted a series of experiments to investigate the anti-diabetic effects of a CM prescription, *hachimiji-jo-ga*, and reported findings for the whole prescription and its constituents as well as for the bioactive compound [59–64]. Other selected CM prescriptions for DN treatments and their respective molecular mechanisms are shown in Table 2. In particular, single herbs (e.g., *Auricularia auricula, hei-mu-er*) and CM prescriptions (e.g., *Danggui Buxue Tang* and *Gui Qi Mixture*) produced better beneficial effects than conventional anti-DN drugs by regulating blood lipid metabolism and lipoprotein lipase activity through the regulation of blood glucose based on their complex compound matrices [65–67]. The changes in blood glucose, triglyceride (TG), total cholesterol (TC), and high-density lipoprotein (HDL) were reversed by *Gui Qi Mixture*, but not by the ACE inhibitor benazepril in diabetic rats [68]. Similarly, the increases in fasting blood glucose (FBG), TG, and TC were attenuated, and the renal kidney/body weight (K/B) ratio, urinary albumin excretion (UAЕ), and creatinine clearance rate (CCr) in STZ-induced diabetic rats were ameliorated after 8 weeks of treatment with *Danggui Buxue Tang* compared with benazepril [69]. Collectively, CMs may exert synergistic effects targeting multiple organs, and benefiting the whole internal milieu of DN patients.

At the ESRD stage, it is almost impossible to prevent the disease from becoming more severe, and dialysis may be the final resort for these patients. To provide a more cost-effective therapeutic approach, other potent remedies are urgently needed. In this regard, the combined
Table 1 Chinese medicines used in the management of experimental diabetic nephropathy

| Species                                      | Medicinal part | Extract/Compound       | DN model | Nephro-protective Mechanisms                                         | Pharmacodynamic indicators                                                                 | Duration | Ref.  |
|----------------------------------------------|----------------|------------------------|----------|------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|----------|-------|
| Eclipta alba (han-lian-cao)                  | –              | Ethanol extract        | STZ rat  | ↓α-glucosidase and aldose reductase activities                         | FBG, HbA1C, urea, uric acid, UCr, insulin                                                | 3 weeks  | [76]  |
| Gymnema montanum Hook (shi-geng-teng)       | –              | Ethanol extract        | ALX rat  | ↓TBARS, hydroperoxides; ↑SOD, CAT, GSH-Px, GST                         | FBG, insulin, urea, Cr, uric acid                                                        | 3 weeks  | [77]  |
| Cinnamomum zeylanicum (vi-kan-rou-gui)       | –              | Aqueous extract        | STZ rat  | ↑UCP-1; GLUT4                                                           | FBG, K/B ratio, insulin, HDL, TC, TG, Cr, histopathology                                | 22 days  | [78]  |
| Panax notoginseng (san-qi)                   | Roots          | Notoginoside           | STZ rat  | ↓VEGF; ↑BMP-7                                                          | Cr, CCr, Ualb                                                                              | 4 weeks  | [79]  |
| Mesona procumbens Hemsl (xiancao)            | –              | Aqueous extract        | STZ rat  | ↑TSP-1                                                                | Body weight, FBG, histopathology                                                        | 4 weeks  | [14]  |
| Piper auritum (hu-jiao)                      | Leaves         | Hexane extract         | STZ rat  | ↓AGEs, serum glycosylated protein, LDL glycation, glycated hemoglobin, renal glucose, thiorbituric acid-reactive substance, ↑SOD, CAT, GPx and GSH | Kidney oxidative stress                                                                 | 4 weeks  | [44]  |
| Smilax thunsonchilifolius (xue-lian)          | Leaves         | Aqueous extract        | STZ rat  | ↓TGF-β1, Smad2/3, collagen III, collagen IV, laminin-1, FN             | FBG, insulin, UAE, Cr, kidney hypertrophy, GBM thickening                               | 4 weeks  | [80]  |
| Milk thistle (nai-ji-cao)                    | –              | Silymarin              | STZ rat  | ↓Lipid peroxidation; ↑CAT, SOD, GPx                                    | FBG, serum urea, Cr, Ualb                                                                | 4 weeks  | [81]  |
| –                                            | –              | Curcumin               | STZ rat  | ↓eNOS, ET-1, TGF-β1, FN, NF-κB, p300                                    | ECM                                                                                       | 4 weeks  | [82]  |
| Allium sativum, (da-suan)                    | –              | –                      | STZ rat  | ↓TBARS, ↑GSH                                                           | FBG, insulin, TG, TC, CCr, UAE, NAG                                                       | 30 days  | [13]  |
| Psidium guajava (fan-shi-liu)                 | Leaves         | Total triterpenoids    | HFD + STZ rat | ↓Hyperglycemia                                                         | FBG, insulin, Cr, BUN, capillary, base-membrane incassation, glomerular swelling, cysts and tubules edema | 6 weeks  | [83]  |
| Panax notoginseng (san-qii)                  | Roots          | Notoginoside           | STZ rat  | ↓TGF-β1; ↑Smad7                                                          | FBG, renal index, CCr, Ualb                                                               | 6 weeks  | [84]  |
| Trigonella foenum-graecum (xiang-cao)         | Seeds          | Aqueous extract        | HFD + STZ rat | ↓MDA, β-hydroxy-2’,-deoxyguanosine, renal cortex DNA; ↑SOD, CAT         | FBG, K/B ratio, Cr, BUN, Ualb, and CCr, GBM                                              | 6 weeks  | [85]  |
| Schisandra chinensis (wu-wei-zi)              | Fruits         | Ethanol extract        | STZ mice | ↓EMT, α-SMA, PAI-1, E-cadherin, Snail; ↑E-cadherin, α-SMA               | ACR, UAE, ECM deposition, podocyte loss and integrity of the slit diaphragm               | 7 weeks  | [21]  |
| –                                            | –              | Curcumin               | STZ mice | ↓COX-2, caspase-3, F- to G-actin cleavage; ↑p38-MAPK, HSP25             | Ualb, ACR                                                                                 | 7 weeks  | [24]  |
| Panax ginseng (ren-shen)                     | –              | Ginsenoside 20(S)-Rg(3) | OLETF rats | ↓TBARS, iNOS, CML                                                       | FBG, CCr, UAE, urine volume                                                               | 50 days  | [18]  |
| Polygonum multiflorum Thunb (he-shou-wu)     | –              | Tetrahydroxystilbene   | STZ rat  | ↓TGF-β1, COX-2, ↑CAT, SOD, GSH-Px, SIRT1                              | TC, TG, BUN, Cr, Ualb, K/B ratio, MDA                                                     | 8 weeks  | [25]  |
| Species                                      | Medicinal part | Extract/Compound                                      | DN model        | Nephro-protective Mechanisms                                                                 | Pharmacodynamic indicators                                      | Duration | Ref.    |
|----------------------------------------------|----------------|------------------------------------------------------|-----------------|------------------------------------------------------------------------------------------------|------------------------------------------------------------------|----------|---------|
| *Paeonia lactiflora Pall.* (shao-yao)        | –              | Total glucosides                                      | STZ rat         | ↓ Macrophages accumulation and proliferation; ↑ p-JAK2, p-STAT3                                | UAlb                                                            | 8 weeks  | [47]    |
| *Aceranthus sagittatus* (yin-yang-hua)       | –              | Icarin                                               | STZ rat         | ↓ MDA, Hyp, TGF-β1, collagen IV; ↑ SOD                                                         | FBG, Cr, BUN, histopathology                                     | 8 weeks  | [86]    |
| *Angelica acutiloba* (dong-gu)               | Roots          | Aqueous ethanol extract                              | STZ rat         | ↓ NF-κB, TGF-β1, FN, AGEs, RAGE                                                              | FBG, UAlb, UAE, Cr, CCR, ECM expansion                          | 8 weeks  | [87]    |
| *Salvia miltiorrhiza* (dan-shen)             | –              | Aqueous extract                                       | STZ rat         | ↓ TGF-β1, AGEs, RAGE, collagen IV and ED-1                                                     | FBG, UAlb, UAlb, UAE                                            | 8 weeks  | [51]    |
| *Tripterygium wilfordii* (lei-gong-teng)     | –              | Multi-glycoside                                      | STZ rat         | ↓ Mesangial cell proliferation, α-SMA, collagen 1                                             | Body weight, UAlb, FBG, Cr, BUN, histopathology                 | 8 weeks  | [88]    |
| *Hibiscus sabdariffa* L (luo-shen-hua)       | Flowers        | Polyphenols                                           | STZ rat         | ↓ TBARS, ↑ CAT and GSH                                                                         | K/B ratio, proximal convoluted tubules, TG, TC, LDL             | 8 weeks  | [89]    |
| *Panax quinquefolium* (xi-yang-shen)         | Roots          | Ethanol extract                                       | STZ+ db/db mice | ↓ Oxidative stress, NF-κB p65, ECM, vasoactive factors                                        | Albuminuria and mesangial expansion                              | 6 and 8 weeks | [90] |
| *Rheum officinale* (da-huang)                | –              | Rhein                                               | db/db mice      | ↓ TGF-β1, FN                                                                                   | UAlb, ECE, TC, TG, LDL-C, Apo E                                 | 8 weeks  | [91]    |
| *Averrhoa carambola L* (yang-tao)            | Roots          | 2-dodecyl-6-methoxy-cyclohexa-2,5-diene-1,4-dione    | KRAy mice       | ↓ Hyperglycemia, AGE, NF-κB, TGF-β1, CML, ↑ SOD and GSH-Px activities                         | Proteinuria, Cr, CCR, serum urea-N, ECM expansion               | 8 weeks  | [17]    |
| *Radix Astragali* (huang-qu)                 | Roots          | Aqueous extract                                      | STZ rat         | ↓ MDA, IL-6, TNF-α, NF-κB, PKCq; ↑ SOD and GSH-Px activities                                 | FBG, body weight, Cr                                            | 60 days  | [42]    |
| *Glycyrrhiza uralensis* (gan-cao)            | –              | –                                                    | STZ rat         | ↓ MDA; ↑ GSH, SOD and CAT                                                                      | FBG, body weight, histopathology                                | 60 days  | [11]    |
| *Acacia nilotica* (jin-he-huan)              | Pods           | Aqueous methanol extract                            | STZ rat         | ↓ Hyperglycemia, IL-1, ICAM-1, NF-κB p65                                                      | FBG, serum urea, Cr, histopathology                              | 60 days  | [28]    |
| *Portulacolaeracea* (ma-chi-xian)            | –              | Aqueous extract                                      | STZ+ db/db mice | ↓ TGF-β1, AGEs, ICAM-1, NF-κB CML, ↑ SOD and GSH-Px activities                               | FBG, Cr, water intake and urine volume                           | 10 weeks | [92]    |
| –                                            | –              | Genistein                                            | STZ rat         | ↓ ICAM-1, gp91 and TBARS; ↑ phospho-tyrosine and phospho-ERK/ERK ratio                      | FBG, insulin, total protein, UAlb, urinary MCP-1 excretion      | 10 weeks | [93]    |
| *Smilax glabra Roxb.* (tu-fu-ling)           | Rhizome        | Astilbin                                             | STZ rat         | ↓ TGF-β1, CTGF                                                                                | Body weight, survival time, FBS                                  | 6 and 12 weeks | [94] |
| *Psidium guajava L.* (fan-shi-liu)            | Fruits         | Aqueous + methanol extract                          | STZ+ db/db mice | ↓ AR activity, ROS, IL-6, TNF-α, IL-1, CML, MDA, A and AGEs; ↑ GSH, CAT, GSH-Px               | Body weight, insulin                                            | 12 weeks | [95]    |
| –                                            | –              | Caffeic acid, ellagic acid                           | STZ mice        | ↓ Sorbitol dehydrogenase, AR, IL-1, IL-6, TNF-α, MCP-1                                     | Body weight, urine volume, insul, FBG, BUN, CCR, HbA1c, UAlb   | 12 weeks | [96]    |
| *Trigonella foenum-graecum* L. (hu-lu-ba)    | Seeds          | Seed powder                                          | ALX rat         | ↓ Glucose, urea, creatinine, sodium, potassium and IL-6 in serum, MDA and IL-6 in kidney; ↑ SOD and CAT activities, GSH | Glomerular mesangial expansion                                   | 12 weeks | [97]    |
| Species                      | Medicinal part | Extract/Compound            | DN model                      | Nephro-protective Mechanisms                          | Pharmacodynamic indicators                          | Duration | Ref. |
|------------------------------|----------------|-----------------------------|-------------------------------|-------------------------------------------------------|-----------------------------------------------------|----------|------|
| Cornus officinalis (shan-zhu-yu) | Fruits         | –                           | HFD + STZ rat                 | ↓ FBG, NAG, mALB, ↑ insulin and Wilms tumor 1 in glomeruli | FBG, mALB, UCr, BUN, NAG, histopathology              | 12 weeks | [19] |
| Euonymus alatus (wei-mao)    | Leaves and branches | Aqueous extract              | Uninephrectomy + STZ rat       | ↓ TGF-β1Blood lipids, UAlb, HbA1c, ECM expansion and glomerulus sclerosis | Blood lipids, UAlb, HbA1c, ECM expansion and glomerulus sclerosis | 12 weeks | [98] |
| Aster koraiensis (zi-yuan)   | Aerial part     | Ethanol extract              | STZ rat                       | ↓ AGES accumulation, Bax, ↑ Bcl-2                    | FBG, HbA1c, UAE, histopathology                      | 13 weeks | [99] |
| Rosa laevigata Michx. (jin-ying-zhi) | Fruits         | Aqueous extract              | STZ rat                       | ↓ MDA, ROS, NF-κB p65, MCP-1, ↑ SOD and antioxidant activities, iκBα | Kidney oxidative stress                             | 24 weeks | [43] |
| Abelmoschus manihot. (huang-zhu-kui) | Flowers       | Total flavone glycosides, hyperoside | STZ rat                       | ↓ Glomerular cell and podocytes apoptosis, caspase-3, caspase-8 | ACR, UAlb                                           | 24 weeks | [46] |

AGEs: advanced glycation end products, ALX: alloxan, AR: aldose reductase, ACR: urinary microalbumin to creatinine ratio, BMP: bone morphogenetic protein, BUN: blood urea nitrogen, CAT: catalase, CCR: creatinine clearance rate, CML: (epsilon)-(carboxymethyl) lysine, CTGF: connective tissue growth factor, ECM: extracellular matrix, ED-1: monocyte/macrophage, ET-1: endothelin-1, EMT: epithelial-to-mesenchymal transition, ERK: extracellular signal-regulated kinases, FBG: fasting blood glucose, FN: fibronectin, GBM: glomerular basement membrane, GLUT: glucose transporter, GSH-Px: glutathione peroxidase, GST: glutathione-S-transferase, HFD: high fat diet, HDL: high density lipoprotein, HSP: heat shock protein, Hxy: hydroxyproline, iK/B: kidney/body weight, LDI: low density lipoprotein, LPO: lipid peroxidation, iNOS: inducible nitric oxide synthase, eNOS: endothelial nitric oxide synthase, NAG: N-acetyl-beta-D-glucosaminidase, NF-κB: nuclear factor κB, MAPK: mitogen-activated protein kinase, mALB: microalbuminuria, MCP: monocyte chemotactic protein, MDA: malondialdehyde, PAI: plasminogen activator inhibitor, ROS: reactive oxidative species, RAGE: receptor of advanced glycation end-products, SIRT3: signal transducer and activator of transcription 3, α-SMA: α-smooth muscle actin, STZ: Streptozotocin, SRT1: Sirtuin 1, SOX: superoxide dismutase, TARS: thiobarbituric acid reactive substances, TGF: transforming growth factor, TG: triglyceride, TC: total cholesterol, TG: triglycerides, HFD: high fat diet.
use of herbs and drugs, and the development of new therapies are receiving increasing attention.

Modern drugs specifically aim to target disease-related molecules through definite pathways, whereas CM aims to exert synergetic effects and benefit the whole internal milieu of patients, leading to the possibility that the combined use of CMs and modern drugs may exert better therapeutic effects on diseases, especially for chronic and comprehensive DN. Currently, the combined use of herbs and drugs in the treatment of DN has been well-investigated. For example, the CM prescription tangshenling was combined with telmisartan to treat 80 patients with DN, and exhibited a better effect than telmisartan treatment alone [70]. Basic research corroborated that the tangshenling mixture had a synergetic effect with benazepril through a different signaling pathway, which involved down regulation of atrial natriuretic factor (ANF) in plasma and glucose transporter 1 (GLUT1) in the kidney when treating DN [71]. Herbs may reduce the permeability of the drug into the intestinal tract, and may also affect its metabolism in the liver and cause hypoglycemia. Huang Kui capsule reduced the absorption of glibenclamide and accelerated its metabolism. This herb–drug interaction deserves further research on the herb–drug pharmacokinetic interaction to enhance the therapeutic effects and avoid side effects.

Limitations of this review
In many studies included in this review, the bioactivities of the CMs responsible for the anti-DN effects and their molecular targets were not identified. Phytochemical and molecular biological studies are needed to identify the bioactive constituents and to elucidate the underlying mechanisms. Moreover, this review only focused on
Table 2 Experimental studies on selected CM prescriptions in diabetes nephropathy management

| CM preparations                      | DN model | Nephro-protective mechanisms | Pharmacodynamic indicators | Dosage              | Duration | Ref. |
|--------------------------------------|----------|-----------------------------|----------------------------|---------------------|----------|------|
| Xiao-chai-hu-tang                    | STZ rat  | ↓ TGF-β1, FN, and collagen IV, ↑ BMP-7, SOD | FBG, BUN, SCr, renal hypotrophy | 200 mg/kg b.w      | 4 weeks  | [100]|
| LiuweiDihuang Decoction              | STZ rat  | ↓ MDA, iNOS, tNOS, cNOS, ET-1, ET(A), ↑ NO, MMP-2, MMP-9, GSH-Px, SOD | FBG, plasma insulin level | 5, 10, or 15 g/kg b.w | 4 weeks  | [57] |
| Tangshenling mixture plus benazepril  | STZ rat  | ↓ ANF, GLUT1                | UAE, Ccr, K/B ratio        | 5 g/kg b.w         | 6 weeks  | [71] |
| DongguiBuxue Tang                    | STZ rat  | ↓ TGF-β1                    | K/B ratio, UAE, (β2)-MG concentrations, Ccr, FBG, TC, TG | –                   | 8 weeks  | [69] |
| Tangshenning Recipe                  | STZ rat  | ↓ TGF-β1, Ang II            | FBG, TG, CHO, HDL, SCr, Ccr, BUN, (β2)-MG/K/B ratio, GA | –                   | 8 weeks  | [68] |
| Shenbao Recipe                      | STZ rat  | ↓ CTGF, ↑ MMP-9             | UAlb, FBG, TC, Scr         | 13 g/kg b.w        | 8 weeks  | [102]|
| Wu-ling-san                          | STZ rat  | ↓ NF-kB, TGF-β1, FN, AGES, mitochondrial TBARS, CML | UAE, UAlb, Ccr, mesangial matrix expansion | 2.5 g/kg b.w        | 10 weeks | [103]|
| Zhen-wu-tang                         | STZ rat  | ↓ Ang II, ↑ nephrin, podocin | Body weight, polyurea, UAE, Scr, BUN | 320 mg/kg b.w      | 12 weeks | [72] |
| FufangXuezhuantong Capsule           | HFD + STZ rat | ↓ GSH px, SOD             | UAE, Ccr, mesangial matrix expansion | 450, 900, or 1800 mg/kg b.w | 12 weeks | [104]|
| Hachimi-jio-gan                     | STZ rat  | ↓ AGES, sorbitol            | FBG, UAlb, Ccr, serum glycosylated protein, BUN, serum albumin level, TC, TG, angiotensin II, FN, kidney/body weight, body weight | 50,100, or 200 mg/kg b.w | 15 weeks | [59] |
| Kangen-karyu                         | STZ mouse | ↓ AGES, TGF-β1, collagen IV | FBG, BUN                  | 100, 200 mg/kg b.w | 18 weeks | [58] |
| Hachimi-jio-gan                     | OLETF rats | ↓ NF-kB, TGF-β1, FN, iNOS, cyclooxygenase-2, AGES, TBARS | UAE, Ccr, FBG | 50, 100, or 200 mg/kg b.w | 32 weeks | [61] |
| Yiqiayinhuayutongluo recipe          | HFD + STZ rat | ↑ Nephrin                | FBG, UAlb, 24 h U-nephrin | 0.8 g/kg b.w      | 32 weeks | [105]|

AGES advanced glycation end products, ANF atrial natriuretic factor, Ang II angiotensin II, BMP bone morphogenetic protein, BUN blood urea nitrogen, CCR creatinine clearance rate, CHO cholesterol, CML N(episilondi-carboxymethyl)lysine, CGPR calcitonin gene-related peptide, CTGF connective tissue growth factor, ET endothelin, FBG fasting blood glucose, GA glomerular area, GLUT glucose transporter, TGF transforming growth factor, FN fibrotenic, GSH-Px glutathione peroxidase, HDL high density lipoprotein, HFD high fat diet, K/B kidney/body weight, NF-kB nuclear factor kB, NO nitric oxide, cNOS constitutive nitric oxide synthase, eNOS endothelial nitric oxide synthase, TNF-α tumor necrosis factor-α, UAE urinary albumin excretion rate, CCr creatinine clearance rate, ET-1 endothelin-1, ESRD end-stage renal disease, EMT epithelial-to-mesenchymal transition, ECM extracellular matrix, EMMPRIN extracellular matrix metalloproteinase inducer, ERK extracellular signal-regulated kinases, ED-1 monocyte/macrophage, FBG fasting blood glucose, FBG fasting blood glucose, FN fibrotenic, GA glomerular area, GFR glomerular filtration rate, GMCs glomerular mesangial cells, GMB glomerular basement membrane, GSH-Px glutathione peroxidase, GST glutathione-S-transferase, GLUT glucose transporter, HFD high fat diet, HSP heat shock protein, iNOS inducible nitric oxide synthase, ICAM intercellular adhesion molecule, IGF insulin-like growth factor, K/B kidney/body weight, LPO lipid peroxidation, LPL lipoprotein lipase, LXRX liver X receptor, LDL low density lipoprotein, NAG N-acetyl-b-D-glucosaminidase, eNOS endothelial nitric oxide synthase, nNOS constitutive nitric oxide synthase, tNOS total nitric oxide synthase, MAPK mitogen-Activated Protein Kinase; mALB urinary microalbumin.

Studies using in vitro or in vivo DN models. Results from clinical trials investigating the use of CMs for the treatment of DN are needed to confirm the therapeutic effects of CMs in the future.

Conclusion

CMs provide an alternative for DN management in all stages of experimental DN models, especially in the early and incipient stages of DN, and the synergistic administration of CMs with conventional drugs exhibited better efficacy than drugs alone in DN treatment.

Abbreviations

ANF: atrial natriuretic factor; AGES: advanced glycation end products; Ang II: angiotensin II; ALX: alloxan; AR: aldose reductase; ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blocker; ACR: urinary microalbumin to creatinine ratio; BUN: blood urea nitrogen; BMP: bone morphogenetic protein; CAT: catalase; CCR: creatinine clearance rate; CGPR: calcitonin gene-related peptide; CHO: cholesterol; CTGF: connective tissue growth factor; CML: N(episilondi-carboxymethyl)lysine; DM: diabetes mellitus; DN: diabetic nephropathy; ER: endoplasmic reticulum; ET-1: endothelin-1; ESRD: end-stage renal disease; EMT: epithelial-to-mesenchymal transition; ECM: extracellular matrix; EMMPRIN: extracellular matrix metalloproteinase inducer; ERK: extracellular signal-regulated kinases; ED-1: monocyte/macrophage; FBG: fasting blood glucose; FN: fibrotenic; GA: glomerular area; GFR: glomerular filtration rate; GMCs: glomerular mesangial cells; GMB: glomerular basement membrane; GSH-Px: glutathione peroxidase; GST: glutathione-S-transferase; GLUT: glucose transporter; HDL: high density lipoprotein; HFD: high fat diet; Hyp: hydroxypoline; iNOS: inducible nitric oxide synthase; ICAM: intercellular adhesion molecule; IGF: insulin-like growth factor; K/B: kidney/body weight; LPO: lipid peroxidation; LPL: lipoprotein lipase; LXRX: liver X receptor; LDL: low density lipoprotein; NAG: N-acetyl-beta-D-glucosaminidase; eNOS: endothelial nitric oxide synthase; nNOS: constitutive nitric oxide synthase; tNOS: total nitric oxide synthase; MAPK: mitogen-Activated Protein Kinase; mALB: urinary microalbumin.
microalbuminuria, MDA: malondialdehyde; MMP: matrix metalloproteinase; MCP: monocyte chemotactic protein; OLET: utsuka Long-Evans Tokushima Fatty; PPAR: peroxisome proliferator-activated receptor; PAI: plasminogen activator inhibitor; PK1: protein kinase 1; PGF: prostaglandin F; ROS: reactive oxidative species; RAGE: receptor of advanced glycation end-products; SGK: serum and glucocorticoid induced protein kinase; STZ: streptozotocin; SOD: superoxide dismutase; α-SMA: α-smooth muscle actin; SCR: serum creatinine; TGF: transforming growth factor; CM: Chinese medicine; TARS: thiobarbituric acid reactive substances; TIMP: tissue inhibitor of metalloproteinase; TG: triglyceride; TC: total cholesterol; TSP-1: thrombospondin-1; TXB2: thromboxane B2; UCr: urinary creatinine; β(2)-MG: urine β(2)-microglobulin; UCP: uncoupling protein; UAMb: urinary microalbumin; UPiR: unfolded protein response; UAE: urinary albumin excretion; VEGF: vascular endothelial growth factor.

Authors' contributions
YBZ and SCWT designed and conceived the study. YJL, XCC, SCWS, YBF, and KFL select and analyzed the data. YJL, XCC, SCWS, KFL, and YBF wrote the manuscript. YBZ and SCWT revised the manuscript. All authors agree to be responsible to all aspects of the work to ensure that no questions concerning the accuracy or integrity of the work remain unsolved. All authors read and approved the final manuscript.

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Competing interests
The authors declare that they have no competing interests.

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References
1. Gross JL, de Azevedo MJ, Silveiro SP, Canani LH, Caramori ML, Zelmanovitz T. Diabetic nephropathy: diagnosis, prevention, and treatment. Diabetes Care. 2005;28:164–76.
2. Liu JY, Chen XX, Tang SCW, Lao LX, Sze SCW, Lee KY, Zhang KYB. Edible plants from traditional Chinese medicine is a promising alternative for the management of diabetic nephropathy. J Funct Foods. 2015;14:12–22.
3. Tripathi YB, Yadav D. Diabetic nephropathy: causes and management. Recent Pat Endocr Metabol Immune Drug Discov. 2013;7:57–64.
4. Forbes JM, Fukami K, Cooper ME. Diabetic nephropathy: where heme-dynamics meets metabolism. Exp Clin Endocrinol. 2007;115:69–84.
5. Somania R, Singhai AK, Shigunde P, Jain D. Aegopson racemosus Wild (Liliaceae) ameliorates early diabetic nephropathy in STZ induced diabetic rats. Indian J Exp Biol. 2012;50:469–75.
6. Zelmanovitz T, Gerchman F, Balthazar AP, Thomazzelli FC, Matos JD, Canani LH. Diabetic nephropathy. Diabetol Metab Syndr. 2009;1:110.
7. Shaﬁee G, Khamseh ME, Rezai N, Aghili R, Malek M. Alteration of pulmonary function in diabetic nephropathy. J Diabetes Metab Disord. 2013;12:115.
8. Tachibana H, Ogawa D, Matushita Y, Bruemmer D, Wada J, Teshigawara S, Etchuj C, Sato-Horiguchi C, Uchida HA, Shikata K, Makino H. Activation of liver X receptor inhibits osteopontin and ameliorates diabetic nephropathy. J Am Soc Nephrol. 2012;23:1835–46.
9. Foley RN, Culleton BF, Parfrey PS, Harnett JD, Kent GM, Murray DC, Barre PE. Cardiac disease in diabetic end-stage renal disease. Diabetologia. 1997;40:1307–12.
10. Gilbert RE, Connelly K, Kelly DJ, Pollock CA, Krum H. Heart failure and nephropathy: catastrophic and interrelated complications of diabetes. Clin J Am Soc Nephrol. 2006;1:193–208.
11. Kataya HH, Hamza AA, Ramadan GA, Khasawneh MA. Effect of loricic extract on the complications of diabetes nephropathy in rats. Drug Chem Toxicol. 2011;34:101–8.
12. Sadiq S, Naji AH, Shazad M, Zia A. The renoprotective effect of aqueous extract of Carum carvi (black zeera) seeds in streptozotocin induced diabetic nephropathy in rodents. Saudi J Kidney Dis Transpl. 2010;21:1058–65.
13. Mariee AD, Abd-Allah GM, El-Yamany MF. Renal oxidative stress and nitric oxide production in streptozotocin-induced diabetic nephropathy in rats: the possible modulatory effects of garlic (Allium sativum L.). Biotechnol Appl Biochem. 2009;52:227–32.
14. Yang M, Xu ZP, Xu CJ, Meng J, Ding QG, Zhang YM, Weng Y. Renal protective activity of Hsian-tso extracts in diabetic rats. Biomed Environ Sci. 2008;21:222–7.
15. Orsolic N, Sirovnic M, Lackovic G, Gregoric G. Effect of Croatian propolis on diabetic nephropathy and liver toxicity in mice. BMC Complement Altern Med. 2012;12:117.
16. Yan SJ, Wang L, Li Z, Zhu DN, Guo SC, Ye WF, Yang YF, Cong X, Ma T, Shen PP, Sheng J, Zhang WS. Inhibition of advanced glycation end product formation by Pu-erha tea ameliorates progression of experimental diabetic nephropathy. J Agr Food Chem. 2012;60:4102–10.
17. Zheng N, Lin X, Wen Q, Kintoko, Zhang S, Xu X, Huang J, Huang R. Effect of 2-dodecyl-6-methoxy-4-chexa-2,5-diene-1,4-dione, isolated from Averrhoa carambola L. (Oxalidaceae) roots, on advanced glycation end-product-mediated renal injury in type 2 diabetic WKAy mice. Toxic Lett. 2013;219:77–84.
18. Kang KS, Yamabe N, Kim HY, Park JH, Yokozawa T. Effects of heat-processed ginseng and its active component ginsenoside Rg3 on the progression of renal damage and dysfunction in type 2 diabetic Otsuka Long-Evans Tokushima Fatty rats. Biopharm Bull. 2010;33:1077–81.
19. Liu H, Xu H, Shen C, Wu C. Effect of the best compatibility of components in Comri Fructus on WT1 expression in glomerular podocytes of type 2 diabetic rats with early nephropy. Am J Chin Med. 2012;40:537–49.
20. Tang D, He B, Zheng ZG, Wang RS, Gu F, Duan TT, Cheng HQ, Zhu Q. Inhibitory effects of two major isoflavonoids in Radix Astragali on high glucose-induced mesangial cells proliferation and AGEs-induced endothelial cells apoptosis. Planta Med. 2011;77:729–32.
21. Zhang M, Liu M, Xiong M, Gong J, Tan X. Schisandra chinensis fruit extract attenuates albuminuria and protects podocyte integrity in a mouse model of streptozotocin-induced diabetic nephropathy. J Ethnopharmacol. 2012;141:111–8.
22. Xu DQ, Gao Y, Liu XH. Effects of Rhein on the hypertrophy of renal proximal tubular epithelial cells induced by high glucose and angiotensin II in rats. Zhong Yao Cai. 2010;33:570–4.
23. Xie Y, Wang Q, Liu J, Xie J, Xue K, Tang Q. Dracorhodin perchlorate inhibit high glucose induce serum and glucocorticoid induced protein kinase 1 and fibronectin expression in human mesangial cells. Zhong‑guo Zhong Yao Za Zhi. 2010;35:1996–2000.
24. Ma J, Phillips L, Wang Y, Dai T, LaPage J, Adler SG. Curcumin activates the p38MAPK-HSP27 pathway in vitro but fails to attenuate diabetic nephropathy in DBA2 J mice despite urinary clearance documented by HPLC. BMC Complement Altern Med. 2010;10:67.
25. Li C, Cai F, Yang Y, Zhao X, Wang C, Li J, Jia Y, Tang J, Liu Q. Tetrahydro‑dioxystilbene glucoside ameliorates diabetic nephropathy in rats: involvement of SIRT1 and TGF-beta1 pathway. Eur J Pharmocol. 2010;649:382–9.
26. Lee MJ, Yao YK, Chen K, Lee YC, Chung YS, Tseng YM. Andrographolide and 14-deoxy‑11,12-didehydroandrographolide from Andrographis paniculata attenuate high glucose-induced fibrosis and apoptosis in murine renal mesangial cell lines. J Ethnopharmacol. 2010;132:497–505.
27. Li X, Xiao Y, Gao H, Li B, Xu L, Cheng M, Jiang B, Ma Y. Grape seed proanthocyanidins ameliorate diabetic nephropathy via modulation of levels of AGE, RAGE and CTGF. Nephron Exp Nephrol. 2009;111:e31–41.
28. Omara EA, Nada SA, Farag AR, Sharaf WM, El-Toumy SA. Therapeutic effect of Acacia nilotica pods extract on streptozotocin induced diabetic nephropathy in rat. Phytomedicine. 2012;19:1059–67.
29. Sefi M, Fetouri H, Soudani N, Chtourou Y, Makni M, Zeghal N. Artemisia canepis extract alleviates early diabetic nephropathy in rats by inhibiting protein oxidation and nitrative end-products. Pathol Res Pract. 2012;208:157–62.
30. Wang K, Wu YG, Su J, Zhang JJ, Zhang P, Qi XM. Total glucosides of paenoea regulates JAK2/STAT3 activation and macrophage proliferation in diabetic rat kidneys. Am J Chin Med. 2012;40:521–36.
31. Wang BL, Hu JP, Tan W, Sheng L, Chen H, Li Y. Simultaneous quantification of four active isichanusa lignans from a traditional Chinese medicine Schisandra chinensis (Wuwei) in rat plasma using liquid chromatography/mass spectrometry. J Chromatogr B. 2008;865:114–20.
32. Oblioni LS, Dani C, Furnchal C, Henriques JA, Salvador M. Hepatoprotective, cardioprotective, and renal-protective effects of organic and conventional grapevine leaf extracts on Wistar rat tissues. Anais da Academia Brasileira de Ciências. 2011;83:1403–11.
33. Zhang Q, Xiao L, Li M, Li W, Yu M, Zhang H, Sun X, Mao L, Xiang H. Attenuating effect of Fuzhong Xuehuang Capsule on kidney function in diabetic nephropathy model. J Nat Med. 2013;67:86–97.
34. Wen X, Zeng Y, Liu L, Zhang H, Xu W, Li N, Jia X. Zhenqi recipe alleviates diabetic nephropathy in experimental type 2 diabetic rats through suppression of SREBP-1c. J Ethnopharmacol. 2012;142:144–50.
35. Ke HL, Zhang YW, Zhou BF, Zhen RT. Effects of Danshui BuJue Tang, a traditional Chinese herbal decoction, on high glucose-induced proliferation and expression of extracellular matrix proteins in glomerular mesangial cells. Nat Prod Res. 2012;26:1022–6.
36. Yiu WH, Wong DW, Chan LY, Leung JC, Chan KW, Lai KN, Tang SC. Tissue kallikrein mediates pro-inflammatory pathways and activation of protease-activated receptor-4 in proximal tubular epithelial cells. PLoS ONE. 2014;9:e88894.
37. Lin M, Yi WH, Wu HJ, Chan LY, Leung JC, Au WS, Chan KW, Lai KN, Tang SC. Toll-like receptor 4 promoters tuberculosis inflammation in diabetic nephropathy. J Am Soc Nephrol. 2012;23:88–92.
38. Singh DK, Winocour P, Farrington K. Oxidative stress in early diabetic nephropathy: fueling the fire. Nat Rev Endocrinol. 2011;7:176–84.
39. Chung SSM, Ho ECM, Lam KSL, Chung SK. Contribution of polyl pathway to diabetes-induced oxidative stress. J Am Soc Nephrol. 2003;14:5233–6.
40. Wada J, Makino H. Inflammation and the pathogenesis of diabetic nephropathy. Clin Sci. 2013;124:139–52.
41. Fioretto P, Barzon I, Mauer M. Is diabetic nephropathy reversible? Diabetes. 2014;63:322–38.
42. Gao Y, Zhang RR, Li JH, Ren M, Ren ZX, Shi JH, Pan QZ, Ren SP. Radix Astragali lowers kidney oxidative stress in diabetic rats treated with insulin. Endocrine. 2012;42:592–8.
43. Zhou Y, Liao Q, Luo Y, Qing Z, Zhang Q, He G. Renal protective effect of Rosa laevigata Michx. by the inhibition of oxidative stress in streptozotocin-induced diabetic rats. Mol Med Rep. 2012;5:1548–54.
44. Perez Gutierrez RM, Flores Cotera LB, Gonzalez AM. Evaluation of the antioxidant and anti-glication effects of the hexane extract of Acacia nilotica leaves in vitro and beneficial activity on oxidative stress and advanced glycation end-product-mediated renal injury in streptozotocin-treated diabetic rats. Molecules. 2012;17:11897–919.
45. Yang M, Watanabe M, Shimizu S, Mizuno N, Nakamura T, Ueno H, Nara T, Kato S, Seno M. Attenuation of protease-activated receptor-4 in proximal tubular epithelial cells. PLoS ONE. 2015;10:e0145990.
46. Wang K, Wu YG, Su J, Zhang JJ, Zhang P, Qi XM. Total glucosides of paenoea regulates JAK2/STAT3 activation and macrophage proliferation in diabetic rat kidneys. Am J Chin Med. 2012;40:521–36.
47. Ruggenenti P, Perna A, Remuzzi G. Gruppo Italiano di Studi Epidemiologici in N. ACE inhibitors to prevent end-stage renal disease: when to start and why possibly never to stop: a post hoc analysis of the REIN trial results. ramsipir efficacy in nephropathy. J Am Soc Nephrol. 2001;12:2832–7.
48. Mann JF, Green D, Jamerson K, Riuilope LM, Kurenik SJ, Little T, Viberi G, Group AS. Averasent for overt diabetic nephropathy. J Am Soc Nephrol. 2010;21:527–35.
49. Zheng N, Lin X, Wen QM, Kintoko, Zhang SJ, Huang JC, Xu HY, Huang RB. Effect of 2-dodecyl-6-methylcyclohex-2-ene-1,4-dione, isolated from Averrhoa carambola L. (Oxalidaceae) roots, on advanced glycation end-product-mediated renal injury in type 2 diabetic KK/Ay mice. Toxocoll Lett. 2013;219:77–84.
50. Lee SH, Kim YS, Lee SJ, Lee BC. The protective effect of Salvia mitiorrhiza in an animal model of experimentally induced diabetic nephropathy. J Ethnopharmacol. 2011;137:1409–14.
51. Lee HS, Ku SK. Effect of Picrorhiza Rhizoma extracts on early diabetic nephropathy in streptozotocin-induced diabetic rats. J Med Food. 2008;11:294–301.
52. Zhu B, Wang H. Basic theories of traditional Chinese medicine. Singing Dragon. 2011; p. 21–35.
53. Cusumano AM, Bodkin NL, Hansen BC, Iotti R, Owens J, Klotman PE, Kopp JB. Glomerular hypertension is associated with hyperinsulinemia and precedes overt diabetes in aging rhesus monkeys. Am J Kidney Dis. 2002;40:1075–85.
54. Ohtomo S. The development of novel therapeutic targets for diabetic nephropathy: hyperinsulinemia, HIF-1, and mesangial. Jpn J Vet Res. 2010;58:41.
55. Ji W, Gong BQ. Hypolipidemic activity and mechanism of purified extract of Salvia mitiorrhiza in hyperlipidemic rats. J Ethnopharmacol. 2008;119:291–8.
56. He H, Yang X, Zeng X, Shi M, Yang J, Wu L, Li L. Protective effect of Jiweihuang decoction on early diabetic nephropathy induced by streptozotocin via modulating ET-ROS axis and matrix metalloproteinase activity in rats. J Pharm Pharmacol. 2007;59:1297–305.
57. Okamoto T, Park CH, Noh JS, Torizuka K, Sei Y, Park J, Yokozawa T. Hepato-renoprotective activity of Chinese prescription Kangen-karyu through inhibition of AGE formation and fibrosis-related protein expression in type 2 diabetes. J Pharm Pharmacol. 2011;63:952–9.
58. Yokozawa T, Yamabe N, Cho EJ, Nakagawa T, Gowda S. A study on the effects to diabetic nephropathy of Hachimi-jo-gan in rats. Nephron Exp Nephrol. 2004;97:e38–48.
59. Nakagawa T, Yokozawa T, Yamabe N, Ryhyn DY, Goto H, Shimada Y, Shibahara N. Long-term treatment with Hachimi-jo-gan attenuates kidney damage in spontaneously diabetic WBN/Kob rats. J Pharm Pharmacol. 2005;57:1205–12.
60. Yamabe N, Yokozawa T. Activity of the Chinese prescription Hachimi-jo-gan against renal damage in the Otsuka Long-Evans Tokushima fatty rat: a model of human type 2 diabetes mellitus. J Pharm Pharmacol. 2006;58:335–45.
61. Yamabe N, Kang KS, Goto E, Tanaka T, Yokozawa T. Beneficial effect of Corni Fructus, a constituent of Hachimi-jo-gan, on advanced glycation end-product-mediated renal injury in streptozotocin-treated diabetic rats. Biol Pharm Bull. 2007;30:520–6.
62. Yamabe N, Yokozawa T. Protective effect of Hachimi-jo-gan against the development of pancreatic fibrosis and oxidative damage in Otsuka Long-Evans Tokushima Fatty rats. J Ethnopharmacol. 2007;113:91–9.
63. Yokozawa T, Yamabe N, Kim HY, Kang KS, Hur JM, Park CH, Tanaka T. Protective effects of morroniside isolated from Corni Fructus against renal damage in streptozotocin-induced diabetic rats. Biol Pharm Bull. 2008;31:1422–8.
64. Chen G, Luo YC, Li BF, Li B, Guo Y, Li Y, Su W, Xiao ZL. Effect of polysaccharide from Auricularia auricula on blood lipid metabolism and lipoprotein lipase activity of ICR mice fed a cholesterol-enriched diet. J Food Sci. 2006;71:H103–8.
65. Yuan Z, He P, Cui J, Takeuchi H. Hypoglycemic effect of water-soluble polysaccharide from Auricularia auricula-judae Quell. on genetically diabetic KK-Ay mice. Biosci Biotechnol. Biochem. 1998;62:1898–903.
66. Xuexu Y, Youdi L, Fei H, Lili C, Mingde L. Pharmacological actions of hyphae body of Auricularia auricula L. ex Hook f endows its alco‑hol extract Zhongxue Zhong Yao Za Zhi. 1994;19(4):30–2.
67. Zhang Y, Xie D, Chen Y, Zhang H, Xia Z. Protective effect of Gui Qi mixture on the progression of diabetic nephropathy in rats. Exp Clin Endocrinol Diabetes. 2006;14:563–8.
69. Zhang YW, Xie D, Xia B, Zhen RT, Liu IM, Cheng JT. Suppression of transforming growth factor-beta1 gene expression by Danggui buxue tang, a traditional Chinese herbal preparation, in retarding the progression of renal damage in streptozotocin-induced diabetic rats. Horm Metab Res. 2006;38:82–8.

70. Li J, He XL, Li Q. Clinical study on treatment of early diabetic nephropathy by tangshenling combined with telmisartan. Zhonggguo Zhi Yi He Zhi. 2006;2:415–8.

71. He XL, Li JP, Chen YP, Zhang ZG, Lin WQ, Chen JH. Effects of Tangshen‑ling mixture and benazepril on rats with diabetic nephropathy and its mechanism. Zhong Yi Yi He Xue Bao. 2006;4:43–7.

72. Cai Y, Chen J, Jiang J, Cao W, He L. Shen Y, Fukushima M, Ito Y, Muraki E, Hosono T, Seki T, Ariga T. Verification of the antidiabetic effect of Eclipta alba mixed with the association of alpha‑glucosidase and aldose reductase. Nat Prod Res. 2012;26:2363–7.

73. Ramakumar KM, Ponnampanikar P, Veluthupathrabhu S, Archunan G, Rajaguru P. Protective effect of Gymnema montanum against renal damage in experimental diabetic rats. Food Chem Toxicol. 2009;47:2516–21.

74. Shen Y, Fukushima M, Ho Y, Muraki E, Hosono T, Seki T, Ariga T. Verification of the antidiabetic effects of cinnamon (Cinnamomum zeylanicum) using insulin‑uncontrolled type 1 diabetic rats and cultured adipocytes. Biosci Biotech Bioch. 2010;74:2418–25.

75. Tu Q, Qin J, Dong H, Lu F, Guan W. Effects of Panax notoginseng on the expression of TGF‑beta1 and Smad7 in renal tissues of diabetic rats. J Huazhong Univ Sci Technol. 2011;31:190–3.

76. Honore SM, Cabrera WM, Genta SB, Sanchez SB, Sanchez SS. Protective effect of yacoon leaves decoction against early nephropathy in experimental diabetic rats. Food Chem Toxicol. 2012;50:1704–15.

77. Vessal G, Akmaili M, Najafi P, Meo MP, Sahgehb MM. Silymarin and milk thistle extract may prevent the progression of diabetic nephropathy in streptozotocin‑induced diabetic rats. Ren Fail. 2010;32:733–9.

78. Chiu J, Khan ZA, Farhankhoee H, Chakraborti S. Curcumin prevents diabetes‑associated abnormalities in the kidneys by inhibiting p300 and nuclear factor‑kappa B. Nutrition. 2009;25:964–72.

79. Huang Q, Zhao JJ, Ye CL, Wang JR, Ye KH, Zhang XQ, Wang Y, Ye WC. Nephro‑protective effects of total triterpenoids from Psidium guajava leaves on type 2 diabetic rats. Zhong Yao Cai. 2012;35:94–7.

80. Tu QN, Dong H, Lu FE. Effects of Panax notoginseng on the nephropathy in rats with type 1 diabetes mellitus. Chin J Integr Med. 2011;17:612–5.

81. Xue W, Lei J, Li X, Zhang R. Trigonella foenum‑graecum seed extract protects kidney function and morphology in diabetic rats via its anti‑oxidant activity. Nutr Res. 2011;31:555–62.

82. Qiu MY, Kai C, Liu HR, Su YH, Yu SQ. Protective effect of Icarin on the early stage of experimental diabetic nephropathy induced by streptozotocin via modulating transforming growth factor beta1 and type IV collagen expression in rats. J Ethnopharmacol. 2011;138:731–6.

83. Liu IM, Tzeng TF, Liou SS, Chang CJ. Angelica acutiloba root alleviates advanced glycation end‑product‑mediated renal injury in streptozotocin‑diabetic rats. J Food Sci. 2011;76:H165–74.