Diabetic nephropathy (DN) is one of the main causes of renal end-stage disease. Hyperglycemia may be toxic either by non-enzymatic reaction of glucose with proteins and subsequent formation of advanced glycation end products (AGEs) or by increased metabolism leading to increased oxidative stress and activation of protein kinase C resulting in increased production of cytokines. Angiotensin II (Ang II) stimulates transforming growth factor β1 (TGF-β1) production via the signal transduction pathway and TGF-β1 induced collagen synthesis leading to DN.\(^{(1)}\)

The development of DN is morphologically characterized by progressive thickening of the glomerular basement membrane and expansion of the mesangial matrix, which correlates to glomerular filtration function.\(^{(1)}\)

Tight glycemic control is focused on to reduce the progression of nephropathy complications. Angiotensin-converting enzyme inhibitors (ACEI), Ang II receptor blockers (ARBs) and nondihydropyridine calcium channel blockers (CCBs) have been shown to reduce microalbuminuria and reduce the progression of renal disease in patients with diabetes.\(^{(2)}\)

The pathogenesis of DN is complex. The current treatment is only for a particular cause without multi-target therapeutic drugs. Chinese medicine is a great treasure with multi-component complex drugs interacting with multiple targets and functions. The aim of this paper is to review the protection effect of Chinese medicine for treating diabetic nephropathy in clinical studies, in vivo studies, and in vitro studies. The possible mechanisms, the major compounds and active crude drugs were also summarized. It was shown that Chinese medicine could not only relieve several symptoms and improve the quality of life, but also reduce the levels of proteinuria and kidney damage, and further improve renal function via multiple pathways based on the whole human system. Moreover, there were no reports of severe adverse reactions during the treatment.

**KEYWORDS** diabetic nephropathy, Chinese medicine, in vivo study, in vitro study

**CHINESE HERBAL PREPARATIONS**

**Bawei Dihuang Pill (八味地黄丸, BWDHP)**

**Clinical Study**

Cao, et al\(^{(3)}\) used BWDHP to treat 48 cases of type 2 DN. The patients with type 2 DN were randomly divided into treatment group (27 cases) and control group (21 cases). The control group was treated with regular insulin or Novolin 30R insulin. Captopril was used to treat high blood pressure, and fenofibrate or lovastatin was used to treat high blood lipids. The treatment group was given BWDHP Decoction (one oral dose daily) plus hypoglycemic agents. After a 6-week treatment, the total effective rate of BWDHP treatment group was 85.18%, while the control group was only 66.67%. Significant difference was shown between the two groups (P<0.05). BWDHP could significantly reduce the levels of urinary protein excretion (UPE), serum creatinine (Cr) and blood urea nitrogen (BUN). BWDHP treatment relieved symptoms of fatigue, dry mouth and polyuria. The effect of BWDHP might be due to the reduction of hyperglycaemia.
renal AGEs, expression of TGF-β1, fibronectin, inducible nitric oxide synthase (iNOS) and cyclooxygenase-2. (4)

**In Vivo Study**

In an animal model of insulin-dependent (type 1) DN, in which rats were subjected to sub-total nephrectomy followed by streptozotocin (STZ) injection, BWDHP significantly reduced UPE and BUN levels, and increased Cr clearance rate (CCr) at an oral dose of 50, 100 or 200 mg/kg body weight per day for 15 weeks. The results showed that BWDHP could protect the diabetic kidney by reducing elevated blood glucose, serum triglyceride, total cholesterol concentrations, and serum glycosylated protein; and also by inhibiting lipid peroxidation, and decreasing AGEs formation and sorbitol levels in the kidney. (5)

Otsuka Long Evans Tokushima Fatty (OLETF) rat was a useful animal model of type 2 diabetes with obesity. The model showed clinically relevant phenotypes of diabetes such as hyperinsulinemia, hyperglycemia, insulin resistance, hypertriglycemia, and mild obesity. BWDHP treatment decreased UPE significantly in an early stage, and improved CCr levels at 32 weeks in OLETF rat. (6)

**Major Compounds and Active Crude Drug**

The major compounds of BWDHP extract were morroniside, loganin, and paeoniflorin, while penta-O-galloylglucose, benzoylmesaconine, benzoylpaeoniflorine, 16-ketoalisol A, paeonol, cinnamic acid, and cinnamaldehyde were also observed. *Corni Fructus* was the active crude drug of BWDHP. 7-O-galloyl-D-sedoheptulose was the active component. (7)

**Guanyuan Granule (冠元颗粒, GYG)**

**In Vivo Study**

Chinese prescription GYG consists of the following 6 herbs: *Paeoniae Radix*, *Cnidii Rhizoma*, *Carthami Flos*, *Cyperi Rhizoma*, *Saussureae Radix*, and *Salviae Miltiorrhizae Radix*. In type 2 DN animal studies, following administration of 100 or 200 mg/kg body weight per day of GYG to db/db mice for 18 weeks, serum Cr and BUN levels decreased significantly, and the glomerular enlargement lessened. The mechanism of action may be through down-regulating nuclear factor-kappa B (NF-κ B), cyclooxygenase-2, and iNOS levels, and also through decreasing the serum glucose concentration, and reducing the oxidative biomarkers. (8)

**In Vitro Study**

In an *in vitro* study, GYG significantly inhibited cytotoxicity and the intracellular reactive oxygen species levels, which were induced by high glucose (30 mmol/L) in LLC-PK cells at a concentration of 5, 10 or 50 mg/mL. (9) Furthermore, GYG inhibited the nuclear translocation of NF-κ B at a concentration of 50 mg/mL. (9)

**Guizhi Fuling Pill (桂枝茯苓丸, GZFLP)**

**Clinical Study**

He and Li (10) reported the treatment of 20 cases of type 2 DN patients with GZFLP for 1 month. After GZFLP treatment, 24-h urinary protein, SCr, and BUN decreased significantly, and CCr increased significantly. In comparison with other drugs such as aminoguanidine (an AGES inhibitor), butylated hydroxytoluene (an antioxidant) and captopril (an angiotensin converting enzyme inhibitor), GZFLP’s renoprotective activity was inferior to that of captopril and comparable to that of aminoguanidine. (11)

The effect of GZFLP was due to its ability to lower metabolic abnormalities (the glycation reaction, excessive polyol pathway activity, oxidative stress and lipid metabolic abnormalities) and reduce accumulation of AGEs, triglyceride and total cholesterol levels dose-dependently. (12)

**In Vivo Study**

In a model of type 2 DN, following oral administration of GZFLP to WBN/Kob rats, UPE and serum Cr levels were significantly attenuated. Treatment with GZFLP for 10 weeks in the rats prevented the morphological changes peculiar to DN. GZFLP showed significant reduction of AGEs levels and renal lipid peroxidation levels. GZFLP also reduced fibronectin and TGF-β1 protein expression. (13)

**Huangqi Danggui Mixture (黄芪当归合剂, HQDGM)**

**Clinical Study**

Astragalus membranaceus Bge. and *Radix Angelicae sinensis*, two of the most widely used herbs in Chinese medicine, have been proven to be effective in the treatment of DN. Fifty-four patients with type 2 DN were randomly divided into treatment and control groups. The treatment group was treated with HQDGM (one dose daily), and the control group was treated with losartan (50 mg every day). After a 3 month-treatment, the total effective rate in