Review Article

Herbal Treatment for Renal Diseases

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Abstract

Renal fibrosis is a common consequence of chronic kidney diseases (CKD). Standard therapy to prevent progression of CKD in western medicine includes dietary protein restriction, blood pressure control, angiotensin-converting enzyme inhibition and angiotensin receptor blockade. However, little is known about the renoprotective effects of Chinese herbal medicine. Cumulative evidence suggests that some Chinese herbal medicines, including Astragalus and a mixture of Astragalus plus Angelica, Ligusticum, Triptolide and Rhubarb, have a beneficial role in slowing the progression of CKD. This effect is multi-functional and multi-targeted, and is often associated with a reduction in proteinuria and the amelioration of dyslipidaemia, but not with changes in systemic blood pressure. These mechanisms include anti-inflammation and inhibition of TGF-b overproduction. On the other hand, some Chinese herbal medicines may be hazardous to patients with renal diseases. In this review, we discuss recent advances in the research of some Chinese herbs for pharmacological intervention of progressive renal diseases and kidney-related injuries.

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Introduction

Renal fibrosis is a common consequence of progressive renal diseases. In nearly all cases, the extent of fibrotic lesions strongly correlates with disease severity and eventual progression to end-stage renal disease (ESRD).[1] Modern day therapy of renal disease includes dietary protein restriction, blood pressure control, angiotensin-converting enzyme inhibitors (ACEIs), and angiotensin receptor blockers (ARBs).[2] However, little is known about the renoprotective effects of Chinese herbal medicine. In fact, Chinese herbal medicines have a long history of use in the treatment of various renal diseases. To date, a substantial body of evidence suggests that some Chinese herbs possess a range of important pharmacological properties in retarding progressive chronic kidney disease (CKD). In this review, we discuss recent advances in the research on some of these Chinese herbs for pharmacological intervention in progressive renal diseases and kidney-related injuries as well as the potential for nephrotoxicity from other Chinese herbal medicines.

Pharmacological Treatment in Non-diabetic Chronic Kidney Disease

A. Astragalus membranaceus (Fisch):

*Astragalus membranaceus (*Astragalus, *Huangqi)* is a herb native to northern China and the elevated regions of the Chinese provinces, Yunnan and Sichuan. In Traditional Chinese Medicine (TCM), this drug has been used for the treatment of night sweats, deficiency of *qi* (e.g., fatigue, weakness, and loss of appetite) and diarrhoea.[3] As Astragalus contains numerous active components, including flavonoids, polysaccharides, triterpene glycosides (e.g., astragalosides I-VII), amino acids, and trace minerals,[4] this herb is traditionally prescribed in combination with other Chinese herbal medicines, depending on the desired therapeutic effect and the exact diagnosis. The effects of Astragalus on the reduction of proteinuria and hyperlipidaemia as well as on immune modulation and renoprotection have been studied in patients and experimental animals.

1. Reduction of proteinuria: Most progressive renal

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diseases are accompanied by proteinuria and there are several studies on the use of TCM in its treatment. To explore the therapeutic effect of Astragalus on proteinuria, 30 cases with chronic glomerulonephritis (CGN), including 21 cases with mesangioproliferative glomerulonephritis (MGN) due to IgA nephropathy (IgAN), 8 cases with focal and segmental glomerulosclerosis (FSGS) and 1 case with membranous nephropathy (MN) were enrolled. After treatment with Astragalus injection (40 g/day) for 3 weeks, proteinuria dramatically dropped from 2328 ± 3157 to 1017 ± 765 mg/day.[5] Two other studies in 106 CGN patients have also demonstrated the ability of Astragalus to significantly reduce proteinuria.[6,7] Clinical studies[8-10] have also shown that either Astragalus or Astragalus in combination with Angelica *(Angelica sinesis)* and Ligustrazine[11] not only improved clinical symptoms, increased serum albumin and lowered blood lipid level, but also reduced urinary protein excretion.

In addition, studies of glomerulonephritis in animal models, including immune complex nephritis[12] and adriamycin-induced nephrotic syndrome,[13] have demonstrated that Astragalus reduces proteinuria. As proteinuria is not only regarded as a marker for significant renal injury, but also as a contributor to the renal pathologic injury itself,[14] the effects of Astragalus in reducing the level of proteinuria may have benefits in slowing the progression of CKD.

2. Hyperlipidaemia of nephrotic syndrome: Disorders of lipid metabolism may also enhance the renal injury in CKD. Most studies[15] have shown that Astragalus alone or combined with other herbs such as Angelica, Ligusticum *(Ligusticum wallichii)* or Schizandrae not only improves oedema, increases serum albumin level and lowers proteinuria, but also reduces serum total cholesterol, triglyceride, low-density lipoprotein (LDL) and very low-density lipoprotein levels. Li et al[16] have demonstrated that Astragalus enhances albumin production in the liver. Astragalus and a mixture of other herbs may improve disorders of lipid metabolism, possibly through up-regulation of gene expression of hepatic LDL-receptor and an increase in the activities of serum lipoprotein lipase and lecithin cholesterol acyltransferase.[17]

3. Immunomodulating effects: There are also data indicating that Astragalus has a beneficial immuno-regulating action. In a study of 28 patients with systemic lupus erythematosus (SLE), natural killer cell activity was significantly lower than in normal controls. Pre-incubation of their peripheral blood mononuclear cells with Astragalus stimulated natural killer cell cytotoxicity in SLE patients and healthy controls.[18] Similarly, a higher blood level of interleukin (IL)-1, IL-6, IL- 8 and tumour necrosis factor (TNF)-α was found in patients with childhood nephrotic syndrome (NS). The increased mRNA expression and production of these cytokines was inhibited more significantly in the prednisone plus Astragalus-treated group than those in the prednisone-treated patients.[19] Conversely, a mixture of Astragalus and 2 other herbs increased resistance to the immunosuppressive effects of cyclophosphamide[20] while stimulating the macrophages to produce IL-6 and TNF-α.[21] Astragaloside IV, an active ingredient extracted from Astragalus, increased T and B lymphocyte proliferation and antibody production in vivo and in vitro, but inhibited production of IL-1 and TNF-α from peritoneal macrophages in vitro.[22]

4. Protective effects against renal damage: To evaluate the potential therapeutic role of Astragalus, 68 patients with CKD [serum creatinine (SCr), 176 to 300 mmol/L; creatinine clearance (CCr), 30 to 50 mL/min] were randomised into 2 groups. Group A (n = 34) was treated with 32 g of Astragalus daily for 1 month while Group B (n = 34) received saline as a control. Average SCr in Group A markedly decreased from 244 ± 51 to 162 ± 63 mmol/L and CCr increased from 37.8 ± 6.2 to 53.4 ± 5.3 mL/min, while no significant change in SCr and CCr was observed in Group B.[23] The effect of Astragalus (40 g/day) on improving renal function was comparable to that of captopril (75 mg/day) in another study.[24]

To explore the underlying mechanisms of these therapeutic effects, we conducted experimental studies and demonstrated that a mixture of Astragalus and either *Angelica sinesis* or ACEI could slow the progression of renal interstitial fibrosis in a rat renal injury model induced by unilateral ureteral obstruction[25] or by peritoneal injection of puromycin.[26] In contrast to the effects of ACEI, there was no change in local renal angiotensin II level in NS rats treated with Astragalus and Angelica. These experimental studies suggest that Astragalus may have a therapeutic effect in retarding progression of CKD, an effect unrelated to inhibition of the local renal angiotensin system.[15]

5. Diuretic effects in nephrotic syndrome and congestive heart failure: Diuretics are often used to treat patients with an expanded blood volume. Although diuretic therapy is generally well tolerated, there is a wide spectrum of adverse effects and biochemical changes. However, both Ma[13] and Wang[15] found that Astragalus improved water and sodium retention and reduced proteinuria in the NS and congestive heart failure rat models without any adverse effects. This effect may be responsible for the improvement in cardiac and renal functions, correction of abnormal mRNA expressions of arginine vasopressin and renal aquaporin 2 and amelioration of the blunted renal response to atrial natriuretic peptide.[13] These data demonstrate that Astragalus is quite different from diuretics in treating oedema.

6. Blood pressure control: Systemic hypertension is

associated with the progression of CKD. ACEIs slow progression not only by the reduction of systemic blood pressure but also by direct intrarenal effects, including favourable changes in glomerular haemodynamics and the reduction of angiotensin-mediated fibrosis.[27,28] Interestingly, both clinical and experimental evidence shows that the effect of Astragalus in the treatment of CKD is not associated with systemic blood pressure control.[5,11,13]

7. Renal ischaemia reperfusion injury: Some experimental studies[29-31] have demonstrated that Astragalus plays a role in attenuating the infiltration of inflammatory cells and promoting recovery from renal ischaemia reperfusion injury in a rat model. Astragalus might have this effect by decreasing plasma malondialdehyde and endothelin-1 levels, and over-expressing intercellular adhesive molecule-1. A mixture of Astragalus and Angelica has been shown to protect the kidneys against ischaemic injury and accelerate functional and histological recovery after acute renal ischaemia reperfusion injury, possibly by increasing the activity of c-Jun N-terminal kinase[32] and inhibiting osteopontin expression.[15]

8. Renal fibrosis: Transforming growth factor beta (TGF-β) is a key regulator that influences the progression of renal fibrosis.[33] To investigate the role of Astragalus and Angelica on TGF-β1 expression, rats with puromycin aminonucleoside-induced NS were treated with a mixture of Astragalus and either Angelica or pravastatin, a HMG-CoA inhibitor. After 10 weeks, in both therapeutic groups, the deposition of renal extracellular matrix (ECM), including type III and IV collagen, fibronectin, laminin as well as the expressions of mRNA and protein of TGF-β1 in glomeruli and tubules, were significantly reduced as compared with controls.[32]

In summary, Astragalus and a mixture of Astragalus and other medicinal herbs such as Angelica or Ligusticum may have a beneficial role in slowing the progression of CKD. This action is multi-functional and multi-targeted. The possible mechanisms include the inhibition of TGF-β1 and osteopontin following reduced infiltration of macrophages and limitation of renal intrinsic cell activation, reduction of proteinuria, and correction of hypoalbuminaemia and hyperlipidaemia. However, long-term observations of the therapeutic role of these herbs and high quality clinical trials are required to confirm their favourable effect. Meanwhile, their underlying molecular mechanisms should be further explored.

B. Tripterygium wilfordii Hook F

Tripterygium wilfordii Hook F (TwHF), is a perennial vine-like member of the Celastraceae plant family; while it has been used as an anti-inflammatory agent in TCM for centuries,[34] it has not been used in treating various glomerulonephritis until recently. A large number of compounds have been identified from the extract of TwHF including diterpenoids, such as triptolide and tripdiolide, alkaloids glycosides, beta-sitosterol and tritoquinones;[34-36] however, triptolide appears to be the major active component.

1. Reducing proteinuria: Eighteen NS patients (8 IgAN, 4 MN, 6 MGN) without haematuria and renal insufficiency received triptolide treatment at a dose of 2 mg/kg/day for at least 4 weeks. Complete remission of NS was achieved in 83.3% (15/18) and proteinuria dropped from 2.34 ± 1.14 to 0.5 ± 0.59 g/day.[37] Its effect of reducing proteinuria in patients with primary MGN,[38] lupus nephropathy (LN)[39] and IgAN[40] was also demonstrated in many other clinical and experimental studies.[41]

2. Renal allograft rejection: A prospective clinical trial of 79 patients with kidney transplantation was performed.[42] After 12 months of follow-up, the frequency of acute allograft rejection was less in the group treated with prednisone, cyclosporine (CsA), azathioprine (AZA) and triptolide (1 or 2 mg/ kg/day) than that with prednisone, CsA and AZA. Dong et al[43] found that triptolide increased the survival rate and survival time of rats with kidney transplantation compared with controls. These clinical and experimental studies suggest that triptolide has a therapeutic role in the prevention of acute allograft rejection.

Induction of apoptosis of activated lymph node cells, but not thymocytes or resting lymphocytes,[44] inhibiting IL-2 production by T or B lymphocytes, and inhibition of proinflammatory factor-induced over-expression of major histocompatibility complex and B-7 molecules in renal tubular epithelial cells[45] and the activity of nuclear factor-kappa B.[46] Triptolide effectively inhibited up-regulation of C3, CD40 and B-7 in human proximal tubular epithelial cells. Moreover, triptolide was more effective than CsA and tacrolimus in inhibiting C3 expression.[47] These data suggest that triptolide is an immunosuppressive agent, which is different from CsA, tacrolimus or glucocorticoid. Because triptolide has potential immunosuppressive and anti-inflammatory properties, TwHF may have a therapeutic role in treating progressive inflammatory renal disease such as IgAN, LN, tubulointerstitial nephritis and chronic allograft nephropathy.

C. Rhubarb

Rhubarb (*Rheum officinale*) has been used as a laxative for many years in TCM. In chemical studies performed on Rhubarb, many ingredients with different pharmacologic actions have been isolated from its root, among which anthraquinone is the most important. More than 20 kinds of anthraquinones have been identified, with emodin (3-methyl-1,6,8-carboxyl-anthraquinone), rhein and aloe-

emodin the most extensively investigated.[48]

1. Slowing the progression of chronic renal disease: To evaluate the therapeutic effectiveness of Rhubarb, a series of perspective clinical and experimental studies have been performed. From 1989 to 1992, 151 chronic renal failure (CRF) patients with initial SCr level of 328 ± 92 mmol/L were enrolled to compare the clinical effectiveness of Rhubarb, an ACEI as well as a combined regimen of Rhubarb and ACEI, captopril. All patients were also kept on a low-protein (0.6 g/kg/day) and low-phosphorus (10 mg/kg/day) diet. After follow-up of an average of 32.5 months (range, 15 to 62), uraemic symptoms of nausea and anorexia improved in most of the treated patients. The frequency of ESRF was 54.3% for the ACEI group, 25.9% for the Rhubarb-treated group, and 13.1% for those receiving the combined regimen.[48] The progression rate of renal failure, calculated by regression of 1/SCr versus time was reduced markedly in both Rhubarb and Rhubarb plus captopril group.[49]

In addition, the effect of Rhubarb on renal fibrosis was observed in 5/6 nephrectomised rats, an animal model typical of CKD progression. By the end of 16 weeks, the survival rate was 75% for the Rhubarb-treated rats, 71% for the enalapril treated group and 61% for the untreated group. Both Rhubarb- and enalapril-treated groups had a lower level of SCr and proteinuria as compared with the controls.[50,51] These studies suggest that Rhubarb could prevent the progression of CRF.

2. Molecular and cellular mechanisms: Experimental evidence suggests that rhein not only antagonises the effect of TGF-β1 in mesangial cells,[52] but also inhibits the hypertrophy of renal tubular epithelial cells and the accumulation of extracellular matrix (ECM) induced by TGF-β1.[53,54] In addition, rhein has a protective effect on endothelial dysfunction by inhibiting overexpression of plasminogen activator inhibitor-1, which is related to the activity of mitogen-activated protein kinase.[54] Another in vitro study demonstrated that emodin not only decreased the gluconeogenesis of tubular cells and the adenosine triphosphate content of epithelial mitochondria, but also suppressed the production of various cytokines from macrophages and human mesangial cells and proliferation of both tubular and mesangial cells.[55] Its action appears to be mediated mainly through the inhibition of gene expression of c-myc and the retardation of cell cycle.[56]

In short, experimental and clinical trials suggest that emodin has a renoprotective effect on the development of CKD. These effects may have resulted from the inhibition of TGF-β activity and cellular metabolism. Rhubarb may prevent progression of CRF by unique and multiple effects on metabolism of renal tubular and mesangial cells. Neither experimental nor clinical studies, however, have demonstrated any antihypertensive effects of Rhubarb, thus being different from that of ACEI.

D. Ligusticum wallichii

A member of the *Umbelliferae* family, *Ligusticum wallichii* is used in TCM for a variety of haematological disorders including ischaemia and thrombosis. Ligusticum's traditional actions include invigorating blood circulation, promoting the flow of *qi*, dispelling wind, and alleviating pain. It is traditionally prescribed for headaches, abdominal pain, arthralgias, and menstrual disorders that are due to blood stasis. Ligusticum's active ingredients include alkaloid, tetramethylpyrazine, ferulic acid (a phenolic compound), chrysophanol, sedanoic acid, and 1% to 2% of essential oils such as ligustilide and butylphthalide.[20,57]

1. Therapy of chronic kidney diseases: The clinical effectiveness of Ligusticum was evaluated in many clinical studies. Two studies[58,59] that included a total of 82 patients with CRF showed that Ligusticum and its active component, sodium ferulate, could improve a patient's clinical condition and lower blood levels of SCr and blood urea nitrogen. A study of 67 CRF patients compared the therapeutic efficacy of ACEI versus a regimen of ACEI plus sodium ferulate.[60] During 30 days of follow-up, reduction in SCr and blood urea nitrogen was only observed in the patients treated with ACEI plus sodium ferulate. In addition, in vivo studies in 5/6 nephrectomised rats[61] demonstrated that sodium ferulate significantly reduced SCr and 24-hour urinary protein excretion and ameliorated renal pathological changes.

2. Reducing proteinuria: A study of 120 patients with primary childhood NS compared the effect of prednisone versus a regimen of sodium ferulate and prednisone. After 20 days of follow-up, patients treated with sodium ferulate plus prednisone showed significantly lower levels of 24-hour urinary protein excretion compared to those treated with prednisone alone (0.4 mg/kg/day).[62] Similar results were found in adult NS patients who had normal renal function[63] and in adriamycin-induced nephritic syndrome model in rats.[64]

3. Molecular mechanisms: Studies on the molecular mechanism of this herb have suggested that sodium ferulate corrects abnormal endothelial gene expression of nitric oxide synthase induced by TNF-α,[65] and inhibits expression of e-selectin and p-selectin in activated human umbilical vein endothelial cells.[66] Reduction in the production of renal TGF-β1 and Smad7 was observed in 5/6 nephrectomised rats treated with sodium ferulate. In addition, in vivo studies demonstrated that ferulic acid is an endothelin antagonist.[67] More importantly, the reduction of proteinuria or improvement of renal functional deterioration induced by Ligusticum is closely associated with the correction of blood endothelial system disorder.[59,67] These

studies suggest that the action of Ligusticum in retarding the progression of CKD might mainly depend on inhibiting endothelin activity.

Pharmacological Treatment in Diabetic Kidney Disease

Nephropathy is a major cause of illness and death in diabetes, and diabetic nephropathy (DN) is the leading cause of ESRD in many Western countries.[68] Major therapeutic interventions that have been investigated include the normalisation of blood glucose control, antihypertensive treatment and dietary protein restriction. It is uncertain whether some Chinese herbal medicines can be used to retard the progression of DN. To evaluate the therapeutic efficacy of Chinese herbs, DN patients with massive macroalbuminuria were treated with Astragalus injection (32 g/day, n = 30) or captopril (75 mg/day, n = 20). After 30 days of follow-up, the 24-hour urinary protein excretion in the Astragalus group dropped from 4.02 ± 2.85 to 2.49 ± 2.23 g/day, while it fell in the captopril group from 2.97 ± 2.09 to 2.59 ± 2.01 g/day.[69] Both Astragalus and captopril have been proven to have similar efficacy against experimental diabetic renal hypertrophy and micro-albuminuria.[70] A similar beneficial effect was also observed in the diabetic nephropathy patients receiving another treatment of Astragalus combined with Tetramethylpyrazine daily for 2 to 4 weeks.[71]

To explore the therapeutic effectiveness of rhein, studies were conducted in many animal models of DN, including that in streptozotocin-induced rats,[72] rats on high-lipids and high-sucrose diets,[73] non-obese diabetic mice[74] and C57BL/KsJ db/db mice.[75] Treatment with rhein for 12 weeks markedly decreased the concentration of plasma triglyceride and cholesterol and body weight, but did not improve hyperinsulinaemia. In addition, 24-hour urinary albumin excretion was decreased and renal injury progression delayed in the rhein-treated diabetic db/db mice as compared with the untreated mice. Glomerular hypertrophy, mesangial expansion, thickened basement membrane and excessive matrix accumulation were also ameliorated by rhein. These studies demonstrate that rhein retards the progression of type 2 DN and that Astragalus and rhein together could exert a protective effect on diabetic renal damage.

To investigate the effects of sodium ferulate on early DN, 90 type 2 diabetic patients with microalbuminuria were randomised to routine therapy or sodium ferulate. After 42-weeks of sodium ferulate, urinary albumin excretion rate was markedly decreased and dyslipidaemia significantly improved in the treated group as compared with the routine treatment group.[76] In a group of 24 DN patients with severe renal insufficiency, intervention with piperazine ferulate (600 mg/day) for 3 months also decreased the amount of proteinuria from 3.84 ± 1.7 to 1.82 ± 0.89 g/day, and SCr level was reduced from 281 ± 183 to 185 ± 104 mmol/L.[77]

Glucose transporter-1(GLUT1) is a membrane- embedded protein that mediates the uptake of glucose into the cells.[78] TGF-β1 stimulates glucose uptake by enhancing the expression and function of GLUT1 in cultured mesangial cells,[78] resulting in excessive glucose consumption and ECM production in diabetic nephropathy. Hexosamine biosynthesis pathway plays a role in the development of insulin resistance.[79] The mesangial cell activity of fructose 6-phosphate aminotransferase, a rate-limiting enzyme of the hexosamine pathway, was inhibited by rhein.[80] It may contribute to reducing the mesangial cell hypertrophy and ECM production. In vitro studies also show that human kidney fibroblast cells pre-incubated with high glucose concentration could evoke overexpression of TGF-β1 mRNA, which was inhibited by exogenous hepatocyte growth factor (HGF). Because Astragalus[33] has a pharmacological effect of up-regulating mRNA expression of HGF, it may also retard the progression of diabetic renal damage.

These experimental studies taken together with the clinical data suggest that Astragalus, Rhubarb and Ligusticum have a therapeutic effect on DN. Unfortunately, the observation period has been rather short in nearly all the studies and it is uncertain whether these Chinese herbal medicines can be used to treat or retard the progression of DN.

Herb-related Nephrotoxicity

As Chinese herbal medicine becomes increasingly widely practiced worldwide,[81] reports of adverse effects occasionally appear in the literature and questions are being asked about safety. The use of botanical medicine is ancient, and plant chemicals are still the backbone of our pharmacopoeia because more than 50% of drugs used in Western pharmacopoeia are isolated from herbs or derived from modification of chemicals first found in plants.[82,83] Plants can contain pharmacologically useful and active compounds, but unsurprisingly, they can also contain toxic substances. For instance, one of the most serious recent occurrences of toxicity involving Chinese herbs came to light between 1991 and 1992 in Belgium, where a series of young women were admitted to hospitals with renal failure.[84] However, not all Chinese herbs are toxic to the kidney.

The LD50 of Astragalus is approximately 40 g/kg when administered by intraperitoneal injection to a rat model. Rats had no adverse effects when given doses as high as 100 g/kg of the raw herb by gavage.[20] The LD50 of *Rheum rhaponticum* is more than 5 g/kg when administered by intravenous injection, and more than 10 g/kg when ingested.[20] An ingested overdose of Rhubarb may induce

diarrhoea. Ligusticum is prescribed in traditional Chinese decoctions at dosages of up to 9 g administered over several days. Overdose symptoms may include vomiting and dizziness. According to our knowledge, renal injury related to Astragalus, rhein, and Ligusticum has not been documented so far. To observe the adverse effects of TwHF, 79 CKD patients with normal renal function and diagnosis proven by renal biopsy were enrolled.[38] After a median of 19.3 months of follow-up, temporal mild elevation of SGPT (25.3%), SGOT (6.3%), gastrointestinal symptoms (7.6%) and abnormal menstruation in female patients (8%) were found. No respiratory infection, leukopenia and renal failure were observed. These adverse effects disappeared after withdrawal of the ingestion of TwHF. These data suggest that the Chinese herbal medicines described herein, when administered at therapeutic doses, are safe and do not result in nephrotoxicity.

Conclusions

In summary, cumulative evidence suggests that some Chinese herbal medicines, including Astragalus and a mixture of Astragalus plus Angelica, Ligusticum, Triptolide and Rhubarb have a beneficial role in slowing the progressive renal disease. Their use is often associated with a reduction in proteinuria and the amelioration of dyslipidaemia, but not with changes in systemic blood pressure. The mechanisms are multiple and include anti-inflammation and inhibition of TGF-β overproduction. Though TCM may be a promising new way to prevent the progression of renal fibrosis, few long-term studies evaluating their therapeutic efficacy or high quality clinical trials have been conducted. Such studies are nevertheless required to confirm the positive effects of these herbs. While not all Chinese herbs are toxic to the kidney, herbal medicines may be hazardous to patients with renal diseases because they may interact with other drugs or contain significant amounts of potassium and heavy metals. The frequency of herb-related nephrotoxicity could be markedly reduced if the herbs are prescribed strictly according to the recommendation of the pharmacopoeia with attention to its origin, dose, way of preparation, and duration of intake. It is obvious that traditional herbal medicines, though natural, are not necessarily safer to use than Western ones. The safety of these Chinese herbs needs to be strictly and individually evaluated.

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