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Therapeutic use of traditional Chinese herbal medications for chronic kidney diseases

Yifei Zhong¹, Yueyi Deng¹, Yiping Chen¹, Peter Y Chuang², and John Cijiang He²

¹Department of Nephrology, Longhua Hospital, Shanghai University of Traditional Chinese Medicine, Shanghai, China

²Division of Nephrology, Department of Medicine, Mount Sinai School of Medicine, NY, USA

Abstract

Traditional Chinese herbal medications (TCHM) are frequently used in conjunction with western pharmacotherapy for treatment of chronic kidney diseases (CKD) in China and many other Asian countries. The practice of traditional Chinese medicine is guided by cumulative empiric experience. Recent *in vitro* and animal studies have confirmed the biological activity and therapeutic effects of several TCHM in CKD. However, the level of evidence supporting TCHM is limited to small, non-randomized trials. Due to variations in the prescription pattern of TCHM and the need for frequent dosage adjustment, which are inherent to the practice of traditional Chinese medicine, it has been challenging to design and implement large randomized clinical trials of TCHM. Several TCHM are associated with significant adverse effects, including nephrotoxicity. However, reporting of adverse effects associated with TCHM has been inadequate. To fully realize the therapeutic use of TCHM in CKD we need molecular studies to identify active ingredients of TCHM and their mechanism of action, rigorous pharmacologic studies to determine the safety and meet regulatory standards required for clinical therapeutic agents, and well-designed clinical trials to provide evidence-based support of their safety and efficacy.

Keywords

Kidney disease; Chinese herb medications; toxicity; alternative medicine; drug discovery

Introduction

Corticosteroid and immunosuppressive medications are cornerstone therapies for glomerular diseases. However, these medications are associated with serious side effects. Furthermore, resistance to therapy and relapse of disease after medication discontinuation are common.

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Corresponding authors: John Cijiang He, MD/PhD, Division of Nephrology, Box 1243, Mount Sinai School of Medicine, One Gustave L Levy Place, New York NY 10029, Tel: 212-659-1703, Fax: 212-987-0389, cijiang.he@mssm.edu, Yifei Zhong, MD/PhD, Department of Nephrology, The Shanghai Longhua Hospital, The Shanghai University of Traditional Chinese Medicine, Tel: 086-021-64385700, yifeilily@126.com.

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For patients with chronic kidney disease (CKD), modulation of the renin-angiotensin axis provides only partial salutary effects and does not necessarily prevent the progression to end stage renal disease and the need for renal replacement therapy¹. The lack of therapeutic options for CKD has prompted patients in China and other Asian countries to seek out alternative treatment such as traditional Chinese herbal medications (TCHM).

The practice of traditional Chinese medicine (TCM) is largely guided by the cumulative empirical experience of its practitioners. Although many small clinical studies suggest a therapeutic potential for TCHM in CKD, large randomized trials are lacking. Some TCHM are known to cause nephrotoxicity, which are often overlooked by some physicians and patients because of the incorrectly held belief that herbal medications are innocuous. Another major concern is that the active component(s) in most TCHM formulae and their underlying mechanism of action remain unidentified. Despite these concerns, significant progress has been made in the past decade. However, recent reviews of this topic in the English language are limited²⁻⁴.

In the current review, we reviewed the current knowledge of TCHM for treatment of CKD based on publications in peer-reviewed journals of the English language. We also render a prospective on the direction of future investigation. Our target audience includes clinical nephrologists who care for patients being treated with TCHM and basic scientists who are interested in the drug discovery pertaining to TCHM.

General therapeutic principles of traditional Chinese medicine

The overarching principle in the practice of TCM is the focus on individual assessment and treatment to coordinate the natural balance of the Ying and Yang, which are two major opposing forces of the body represented in the ancient Chinese Taoism philosophy. TCM posits that disease of the body arises from an imbalance within the body and between the body and the nature leading to an alteration in the entire body system.

The syndrome differentiation and treatment (SDAT) approach is a principle that has been used to understand, diagnose, and treat diseases based on the theories of TCM. The diagnostic procedure involves an analysis of the clinical data regarding symptoms, physical signs, and disease history, together with information obtained from application of the four diagnostic methods, which consist of inspection, auscultation and smelling, inquiry, and pulse-taking and palpation (see Table 1). These four diagnostic methods allow the differentiation of syndromes, which in turn dictates the approach to clinical treatment. The patient's response to a specific clinical treatment plan then informs the correctness of the deduced differentiation. These three key aspects of the SDAT approach form the basis of diagnosis and treatment in TCM.

In the practice of TCM, it is generally considered that multiple herbal medications are more effective than a single herbal agent. Therefore, prescriptions of TCHM usually combine several herbs in which a few components contribute to the main effect of the prescription; and these herbs are referred to as “ruler drugs”. In addition, another group of herbs known as “minister drugs” provide an additive effect to the “ruler drugs”, and the remaining constituents of the herbal prescription are called “assistant drugs and messenger drugs”.

Physicians practicing TCM usually prescribe a formulas that combines several types of herbs or minerals where one herb represents the principal component and others serve as adjunctive agents assisting the effects or facilitating the delivery of the principal component. In China, more than 3,200 herbs and 300 mineral and animal extracts are used in more than 400 different formulae⁵. Adjustment of individual components of the herbal prescription by the practitioner is based on patients' signs and symptoms with an overall goal of restoring the balance of Ying and Yang. At each follow-up visit, physicians usually change either the herbal components or their relative percentage in the prescription.

Differences in the practice and principles of TCM and western medicine are summarized in the Table 1. These differences largely stemmed from their different historical background. Concepts of TCM related to organ function, disease pathogenesis, and treatment approach were formulated in the absence of our current molecular understanding of disease and deeply influenced by social, religious and cultural factors in these historical periods. One can debate the validity and scientific merits of the TCM approach. However, one should not immediately discount the empiric knowledge accumulated over centuries of treating patients with different decoctions of herbal mixtures. With recent integration of TCM and western medicine, diagnosis of CKD by practitioner of TCM has supplemented traditional diagnostic approach with western molecular and imaging diagnostic tools. The current treatment of CKD in TCM is often achieved by combining TCHM and western pharmacologic agents. Due to the rapid economic growth and scientific development over last decade, Chinese government has supported studies to examine the scientific basis of TCM using advanced cell and molecular biology approaches. A rapid development of TCM is expected over the next decade.

Treatment of kidney disease with traditional Chinese herbal medications

The therapeutic principles of TCM for CKD include “replenishing vital energy and nourishing blood”, “clearing heat and eliminating dampness”, and “coordinating Yin and Yang in the body”⁶. Hundreds of herbs used in prescriptions of a single herb, decoctions of multiple herbs, or patent medicines have been used to treat patients with CKD. These prescriptions have effects including promotion of diuresis, reduction of proteinuria, and improvement of renal function^{2,7}. Mechanisms of action have been studied for some herbs. Their effects are mainly related to anti-inflammation, anti-oxidative, anti-fibrosis, regulation of immune system, anticoagulation, and improvement of metabolic disturbance^{2,3}. Active ingredient purified from herbs that been studied in CKD include saikosaponin a/d and triptolide. However, the active compounds in many decoctions or patent medications are still unknown and clinical trials demonstrating their efficacy for treatment of CKD are limited. We have summarized current evidence supporting TCHM in treatment of CKD. Key findings from *in vitro* studies, animal models, and human trials are included in Table 2.

1. Astragalus and decoction of Astragalus with Angelica sinensis—The medicinal herb *Astragalus* is derived from the root of *Leguminosae* plant *Astragalus membranaceus* or *Astragalus mongholicus*. It contains more than 60 components including polysaccharides, saponins (astragalosides I-VII), flavonoids, amino acids, and trace

elements⁸. *Astragalus* is traditionally used either alone or in conjunction with another Chinese herb, *Angelica sinensis* to treat patients with CKD².

Mechanisms of action: Pharmacological studies have shown that several compounds from *Astragalus* exhibit multiple effects including stimulation of the immune system, diuresis, antioxidation, and anti-inflammation^{9,10,11}. In addition, *Astragalus membranaceus* has been shown to attenuate podocyte injury induced by complement membranous attack complex¹². In a recent study, effects of Astragaloside IV were analyzed systemically using a computer-assisted target identification program, which identified 39 putative targets including calcium influx inhibition, vasodilatation, anti-thrombosis, anti-oxidation, anti-inflammation, and immune regulation¹³.

Animal studies: The biological effects of *Astragalus* has been investigated in several animal models of kidney disease including 5/6 nephrectomy¹⁴, doxorubicin-induced nephropathy¹⁵, unilateral ureteral obstruction¹⁶, glomerulonephritis¹⁷, and streptozotocin-induced diabetic nephropathy (DN)¹⁸. The results from these studies suggest that *Astragalus* treatment reduces proteinuria and attenuates kidney injury. These effects are associated with inactivation of free radicals, inhibition of nitric oxide synthesis, and reduction of tumor necrosis factor α (TNF- α) production^{15,17,18}. A decoction of *Astragalus* with *Angelica sinensis* has also been shown to attenuate renal interstitial fibrosis in rats with chronic puromycin aminonucleoside nephrosis and obstructive uropathy by suppressing TGF- β 1 expression, macrophages infiltration, and ROS production, and promoting ECM degradation^{14,19-21}.

Clinical studies: *Astragalus* has been used by itself or as one of the “ruler drugs” in decoctions to treat CKD. Several small clinical studies published in Chinese language journals suggest that *Astragalus* decreases proteinuria and improves the plasma levels of total cholesterol and albumin in patients with nephrotic syndrome. In a systematical review of randomized and semi-randomized trials using *Astragalus* for the treatment of DN, 21 randomized-controlled and 4 case-controlled studies with a total of 1804 patients (945 in the treatment group and 859 in the control group) were included. The authors of the systematic review concluded that *Astragalus* is able to improve renal function and reduce proteinuria in patients with DN²². In another meta-analysis of patients with DN, significant beneficial effects on glomerular filtration rate, urinary albumin excretion rate, and thickness of the glomerular basement membrane were observed in the *Astragalus*-treated group compared to the control group²³. Unfortunately, in these two studies the authors could not carry out a systematic review on adverse effects due to the lack of report on severe side effects in all the clinical trials involved. Success treatment of patients with nephrotic syndrome using *Astragalus* has also been reported. For example, a 77-year-old woman with idiopathic membranous nephropathy and nephrotic syndrome who had developed treatment failure with angiotensin converting enzyme inhibitors, angiotensin receptor blockers, cyclosporine A, and mycophenolate mofetil, responded to *Astragalus membranaceus* at a dose of 15 g/d with remission of proteinuria²⁴. No side effects were reported in this patient.

Side effects: *Astragalus* is generally considered safe for most adults. Side effects that can be exclusively ascribed to *astragalus*, however, are not well characterized because it is generally used in combination with other herbs. *Astragalus* is known to inhibit CYP3A4 and can affect the metabolism of certain drugs metabolized by this enzyme²⁵. For example, *astragalus* was reported to reduce cyclophosphamide-induced immunosuppression²⁶. From the above meta-analysis, it is important to note that adverse effects of TCHM have been underreported in clinical trials and this should be corrected in the future studies.

2. Rheum palmatum L and its components: emodin and rhein—The medicinal herb rhubarb is derived from the root of the *Rheum palmatum L* plant. Studies of inorganic elements in rootstocks of *Rheum australe* by atomic absorption spectrophotometry identified 19 elements including more than 20 types of anthraquinones, in which emodin (3-methyl-1,6,8-carboxyl-anthraquinone), rhein, and aloe-emodin have been studied extensively^{27,28}.

Mechanisms of action: The strong cathartic actions of rhubarb are thought to increase the excretion of waste products, including nitrogenous waste accumulated in patients with renal failure, through the intestines²⁹. Hence, rhubarb has been used to treat patients with renal failure. Recently, emodin, an active compound of rhubarb, has been shown to inhibit the lipopolysaccharide (LPS)-induced expression of TLR4 and down-regulate TNF α and IL-6 synthesis in renal tubular epithelial cells³⁰. Emodin has also been shown to inhibit the differentiation and maturation of dendritic cells and increase the number of regulatory T cells³¹. These studies suggest that emodin has a major role in the regulation of inflammation and immune response. Rhein, another active compound of rhubarb, has been shown to improve cell metabolism through glucose transporter 1 and decreases mesangial cell hypertrophy and extracellular matrix synthesis³². These results indicate that active ingredients in rhubarb have multiple mechanisms of action that could improve CKD.

Animal studies: Zhang and El Nahas examined the effect of a rhubarb extract on the development of renal failure in Wistar rats with 5/6 nephrectomy³³. Rhubarb extract treatment decreased proteinuria and glomerulosclerosis compared with no treatment. Treatment of *db/db* diabetic mice using rhein, an active compound of rhubarb, has been shown to decrease the levels of extracellular matrix (ECM) and expression of transforming growth factor (TGF) β -1 and fibronectin in the kidney³⁴. In addition, combination therapy with rhein and an angiotensin converting enzyme inhibitor (ACEI) in *db/db* mice provided additional renal protection that was more than either therapy by itself, as reflected in the reduction of urinary albumin excretion and improvement of renal function and histology³⁵.

Clinical studies: Clinical studies on the effects of rhubarb in patients with CKD have been reported in Chinese medical journals and summarized in an English review article²⁷. These studies suggest that rhubarb is able to reduce proteinuria and improve renal function by itself and may also cause further reduction of proteinuria and improvement of renal function when used together with ACEIs. A recent meta-analysis of clinical studies of rhubarb, which included seven studies that compared *Rheum officinale* (rhubarb root) against no treatment and two studies that compared rhubarb against captopril, found that *Rheum officinale* had a

beneficial effect on renal function compared with no treatment, but was not superior to captopril treatment³⁶. The effect of treatment on all-cause mortality was not available from those studies. Only minor adverse events were reported in association with *Rheum officinale*. Diarrhea was reported in two-thirds of patients when the initial dose of Rheum officinale was greater than 3 g/day but resolved when the dosage was reduced. Standardized monitoring or voluntary self-reporting was not undertaken. Authors of the meta-analysis concluded that all nine studies are low quality and available evidence supporting the use of *Rheum officinale* in patients with CKD is scant.

Side effects: The major side effects of Rheum include nausea, vomiting, diarrhea, and abdominal pain. Long-term use of Rheum could cause electrolyte disorders and liver toxicity³⁷.

3. Decoctions of *Radix bupleuri* and components of *Radix bupleuri*

(Saikosaponin a and d)—Saireito is a combination of twelve herbs of which *Radix bupleuri* is a major component. Saireito has been used in China and Japan for treatment of kidney diseases. Saikosaponin a (SSa) and its epimer saikosaponin d (SSd) are major triterpenoid saponin derivatives found in *Radix bupleuri*, which has been used for treatment of various inflammation-related diseases³⁸. The phytochemistry and pharmacology of *Radix bupleuri* has been reviewed³⁹.

Mechanism of action: Saireito suppresses inflammatory⁴⁰ and proliferation of mesangial cells⁴¹. Both SSa and SSd have been shown to inhibit the expression of inducible nitric-oxide synthase (iNOS), cyclooxygenase-2 (COX-2), tumor necrosis factor (TNF)- α , and interleukin (IL)-6 in lipopolysaccharide (LPS)-stimulated RAW264.7 cells⁴². SSd inhibited mesangial cell proliferation and matrix synthesis⁴³. Saikosaponins also suppressed the proliferation of human T cells by inhibiting nuclear factor (NF)- κ B, NFAT, and AP-1 (c-Fos) signaling pathways⁴⁴. In addition, both in vivo and in vitro studies confirmed that saikosaponins exhibit potent anti-inflammatory and immune-modulatory activities³⁹.

Animal studies: Saireito prevented mesangial cell proliferation in a rat model of mesangio-proliferation glomerulonephritis⁴⁵. Saireito also decreased urinary protein excretion in a rat model of subtotal nephrectomy^{46,47}. However, Saireito did not provide any additional benefit when added to enalapril for renal protection in rats with subtotal nephrectomy⁴⁸. Saireito has also been shown to reduce gentamicin-induced nephrotoxicity in rats⁴⁹ and in MRL/lpr mice⁵⁰. In a rat model of mesangioproliferative glomerulonephritis induced by anti-Thy1 monoclonal antibody, SSd attenuated the amount of proteinuria, increase in systolic blood pressure, accumulation of extracellular matrix, formation of glomerular crescents and infiltration of macrophages and CD8+ T lymphocytes⁵¹. SSd was also able to lessen proteinuria in a rat model of aminonucleoside-induced nephropathy⁵².

Clinical studies: In a randomized controlled study investigating the efficacy of saireito in a pediatric population with IgA nephropathy, 101 patients received either saireito or no treatment for 2 years⁵³. Urinary protein excretion and hematuria were significantly reduced in the saireito group, but remained unchanged in those who did not receive saireito. Proteinuria normalized in 46% of the patients in the saireito group compared with 10% in

those in the untreated group. So far no clinical study of SSa or SSd for treatment of CKD has been published.

Side effects: Radix bupleuri use is known to cause interstitial pneumonia, elevated LFTs and jaundice, edema and hypertension, cystitis, and gastrointestinal symptoms such as nausea, vomiting and diarrhea. However, these symptoms are often associated with overdose and prolonged use of Radix bupleuri⁵⁴. It has also been reported that Saireito occasionally causes side effects such as immunodeficiency, gastro-duodenal ulcer and osteoporosis that are often associated with long-term administration of corticosteroids⁵⁵. Drug-induced pneumonitis and drug-induced acute hepatitis have been also reported with Saireito treatment^{56,57}. However, the side effects of these TCHM are usually underreported in clinical trials. Saireito is a combination of twelve herbs, which immediately raises the question of pharmacological interactions among them and toxicity induced by each of them. Therefore, this drug will be difficult to be approved by the current regulation of drug administration.

4. Cordyceps sinensis and its component H1-A—*Cordyceps sinensis* (Cs) is a blade-shaped fungus that derives its nutrients from larvae of *Lepidoptera*⁵⁸. Its secondary metabolites are cyclic peptides and H1-A⁵⁹. Cs was described in the old Chinese TCM textbook to treat patients suffering from urinary disturbance and edema 2000 years ago. Although kidney disease was not described at that time, these symptoms are considered to be kidney specific based on the TCM theory.

Mechanism of action: *In vitro* studies showed that both aqueous extracts of the whole fruiting body of *Cs* and purified polysaccharides from *Cs* have potent antioxidant activity⁶⁰. *Cs* extracts also inhibited proliferation of cultured mesangial cell⁶¹⁻⁶³.

Animal studies: Shahed et al examined the renal protective effects of a hot water extract of the powdered *Cs* in a rat model of kidney ischemia/reperfusion injury⁶⁴. Intraperitoneal injection of the *Cs* extract before surgery significantly mitigated the rise in serum creatinine and the increase in mRNA transcripts of inflammatory cytokines, monocyte chemoattractant protein-1, and TNF- α associated with ischemia/reperfusion kidney injury. In a separate study, *Cs* treatment improved the renal function of a murine model for immunocomplex glomerulonephritis (MRL lpr/lpr)⁶⁵. In an IgA nephropathy model, a fractionated crude methanolic extract of the fruiting bodies of *Cs* significantly lessened hematuria and proteinuria and improved kidney histology. Compound H1-A of *Cs*, purified by silica gel column chromatography and high-performance liquid chromatography, also demonstrated renal protection against IgA nephropathy⁶¹. The mechanism of renal protection of *Cs* in the rat 5/6 nephrectomy model of renal injury was examined using nuclear magnetic resonance spectral analysis of the kidneys. *Cs* treatment attenuated glomerulosclerosis and urinary albumin/Cr ratio in 5/6 nephrectomized rats. Metabolic analysis of kidney tissues from 5/6 nephrectomized rats showed changes in the levels of TCA cycle intermediates (fumarate, succinate and malate) and suppression of branched-chain amino acids (valine, leucine and isoleucine) metabolism, which were reversed by *Cs* treatment⁶⁶.

Clinical studies: In a study of 69 renal allograft recipients, Cs reversed cyclosporine nephrotoxicity⁶⁷. In another study of 202 patients receiving standard immunosuppressive medications that were treated with or without Cs, the incidences of chronic allograft nephropathy (CAN) and total urinary protein excretion were significantly lower in the Cs group as compared to the group without Cs treatment⁶⁸. Others have also reported the beneficial effects of Cs in CAN⁶⁹. Several studies in the Chinese medical literature have reported that Cs treatment of patients with AKI or CKD improved kidney function. However, these studies have major methodological flaws including inadequate information on patient follow up, lack of a control group with standardized care, and small number of patients.

Side effects: There are very few reports of adverse reactions in human to Cs, which is available as a dietary supplement. Some patients have reported nausea, dry mouth and stomach discomfort with Cs^{70,71}. However, these adverse reactions are extremely rare.

5. Triptolide (PG-90)—Extracts of *Tripterygium wilfordii Hook F* have been used to treat glomerulonephritis for more than 30 years in China with remarkable antiproteinuric effects. Triptolide, a diterpene triepoxide, is one of the major active components of these extracts. Structural modifications, structure-activity relationships, pharmacology, and clinical development of triptolide have been recently reviewed⁷².

Mechanism of action: Triptolide has potent immunosuppressive, immunomodulatory, and anti-inflammatory effects. Molecular and cellular effects of triptolide have been reviewed⁷³⁻⁷⁵.

Animal studies: Triptolide effectively reduced proteinuria in rats with puromycin-induced nephropathy without affecting the glomerular filtration rate⁷⁶. The antiproteinuric effect was associated with improvement in foot process effacement, a decrease in the podocyte injury marker desmin as well as the restoration of nephrin and podocin expression and distribution. In addition, generation of reactive oxygen species and activation of p38 mitogen-activated protein kinase were suppressed by triptolide in podocytes⁷⁶. Triptolide has also been shown to attenuate kidney injury in an experimental rat model of passive Heymann nephritis⁷⁷. Triptolide also improved renal function by inhibition of cyst growth in kidney-specific Pkd1(flox^{-/-});Ksp-Cre mouse model of autosomal dominant polycystic kidney disease⁷⁸. It is hypothesized that triptolide arrests cellular proliferation and attenuates overall cyst formation by restoring Ca²⁺ signaling in these cells⁷⁹. In *db/db* diabetic mice, albuminuria was markedly attenuated by triptolide treatment, accompanied by alleviation of glomerular hypertrophy and podocyte injury⁸⁰. In addition, inflammation and oxidative stress in the kidneys were also attenuated. Effect of triptolide on glomerular hypertrophy was similar to valsartan, but the effects of triptolide on renal inflammation and oxidative stress were more profound than those of valsartan⁸⁰. In addition, triptolide significantly ameliorated lupus nephritis in (NZB × NZW) F1 mice through suppression of cytokine and chemokine production⁸¹.

Clinical studies: Although extracts of *Tripterygium wilfordii Hook F* and triptolide have been used to treat patients with CKD for many years and multiple successful cases reports

and small clinical studies have been published in Chinese medical journals, no randomized clinical trials have been ever published in English peer-reviewed journals.

Side effects: The major side effects of *Tripterygium wilfordii Hook F* include gastrointestinal disorders, liver toxicity, infertility, and hematopoietic disorder^{82,83}. Animal studies suggest that triptolide treatment is associated with nephrotoxicity⁸⁴. However, in two clinical studies to examine the effects of *Tripterygium wilfordii Hook F* in kidney transplant patients, no significant side effects were observed including nephrotoxicity^{85,87}. These data suggest that *Tripterygium wilfordii Hook F*, when administered at therapeutic dose, is relatively safe. There is currently no data on the adverse events in patients treated with triptolide.

The toxicity of Traditional Chinese herbal Medications

Although the TCHM described above are relatively safe and usually do not cause major toxicity at the therapeutic doses, it is critical for us to recognize that some herbal medications can cause significant toxicity including kidney toxicity⁸⁶⁻⁸⁸. The toxicity of these herbal medications could be caused by inherent herb-induced toxicity or contamination of the herb or extract, or both. It was reported that about 10% of the incident end stage renal disease population in Taiwan is due to Chinese herb nephropathy⁸⁹. The most well described renal toxicity associated with traditional Chinese herbal medication is aristolochic acid induced nephropathy (AAN)^{90,91}. Despite awareness of the toxicity of aristolochic acid, some Chinese herbal preparations may still contain traces of this compound. The pathology of AAN is characterized by extensive renal interstitial fibrosis and tubular atrophy without obvious glomerular injury. Uroepithelial malignancies are commonly observed as a long-term sequelae associated with AAN. A retrospective study of 86 patients with AAN found that 19 patients (22.0%) presented with acute kidney injury, while 67 patients (78%) presented as CKD⁹². Eleven (57.9%) patients with acute kidney injury regained renal function and 27 patients (40.2%) with CKD progressed to end-stage renal disease.

Certain TCHM, including *Dioscorea bulbifera*, *Trichosanthes kirilowii*, *Melia toosendan*, *Cassia angustifolia*, and *Polygonum multiflorum*, are known to cause liver toxicity⁹³. TCHM-induced liver toxicity usually occurs after one to four weeks of therapy and is manifested clinically by fatigue, jaundice, and poor appetite. Significant hematopoietic toxicity has been associated with *Sinomenium acutum*, *mercury sulfide*, and *Psychotria rubra*, which are known to cause thrombocytopenia and hemolytic anemia⁹⁴. However, these side effects are uncommon and mostly occur in susceptible patients with overdose and prolonged use of these herbs.

In addition, concomitant use of herbal prescriptions with western medications could engender serious herb-drug interactions leading to complications by increasing or decreasing the pharmacologic or toxicologic effects of either component. For instance, herbs traditionally used to lower glucose concentrations in diabetes could precipitate hypoglycemia if taken in combination with conventional oral hypoglycemic medications⁹⁵. It is known that reported bleeding complications could occur when warfarin is combined

with either *Angelica sinensis*⁹⁶ or *Salvia miltiorrhiza*⁹⁷. Healthcare providers should also caution patients against mixing herbs and pharmaceutical drugs^{98,99}.

Perspective

TCM is a valuable heritage of human experience. Therapeutic potential of these agents is supported by numerous animal studies. However, available clinical studies are small and well-designed randomized clinical trials are lacking to validate these therapies in patients with CKD. Although the therapeutic efficacy of herbs and herb-derived components has not been rigorously tested in large randomized controlled trials, the cumulative experience of treatment success supports more detail examination of the therapeutic potential of herbal medications in complementing or expanding existing therapies for CKD. Currently, there is inadequate evidence to support the use of traditional Chinese herbal medications in patients with CKD. Major challenges and the direction of future studies in this field are described below and summarized in Figure 1.

1. Isolation of active components of herbs—Natural occurring compounds from plants/herbs are of interest to researchers both in their natural forms and as parent compounds for additional synthetic modification. More than a hundred prescribed drugs in the United States are obtained from natural sources and represent one fourth of the total drugs used¹⁰⁰. Natural compounds currently used in medicine exhibit a wide chemical diversity. These compounds, together with their analogues, demonstrate the importance of compounds from natural sources in modern drug discovery efforts. Isolation of active compounds from herbs used in TCM and study of their molecular mechanisms are highly important in the development of novel, clinically useful drugs for medical therapy including CKD. Many laboratories in China and other countries are actively involved in drug discovery efforts based on herbal medication used in TCM. For example, recent studies using capillary gas chromatography and gas chromatography-mass spectrometry have identified several active compounds with strong anti-oxidant and anti-inflammation activities from *Bupleurum marginatum*¹⁰¹. Another example is the identification of a water-soluble analog of triptolide, named Minnelide, which was recently shown to effectively reduce pancreatic tumor growth and spread, and improving survival in patients¹⁰². The therapeutic effect of Minnelide has not been determined in patients with kidney disease. The structures of some commonly used compounds for CKD are shown in Figure 2.

2. Lack of high quality clinical trials: Controlled randomized clinical studies of traditional Chinese herbal medications are difficult to design and execute for at least two reasons. One, there is a wide variation in the prescription of herbal medicine between physicians for the treatment of the same disease condition. This lack of standardization in prescription precludes direct comparison of treatment efficacy. Two, frequent adjustments of the herbal prescription are made based on patients' symptoms and signs; and these adjustments in prescription are not standardized practice. Although this practice reflects more personalized care, it also renders the application of the gold standard in assessment of therapeutic efficacy, randomized controlled trials, nearly impossible. The only solution is to standardized prescription pattern and dosage adjustment among physicians. At least in the context of a clinical trial, these standardized approaches should be taken during the study.

Furthermore, a recommendation has been developed to improve the reporting of clinical trials using herbal medicine interventions¹⁰³. This should help to consolidate efforts and track available clinic studies. A well-designed prospective randomized clinical trial for TCM was published recently to compare the efficacy and safety of oseltamivir and maxingshiganyinqiaosan in treating uncomplicated H1N1 influenza¹⁰⁴. Recently, a multicenter double-blinded, randomized controlled clinical trial was published to compare the effects of TCHM (a mixed herbal decoction) with benazepril in 578 Chinese patients with CKD stage 3 caused by primary glomerulonephritis¹⁰⁵. Patients were randomly assigned to three groups: patients received TCHM, benazepril, or TCHM combined with benazepril. After 24 week follow up, the authors reported that TCHM combined with benazepril can ameliorate renal function and decrease proteinuria synergistically in these patients. Several well-designed prospective randomized clinical trials are currently ongoing in China to study TCHM in patients with CKD.

3. Mechanistic analysis of active compounds using modern approaches—

Experiences from TCM practices strongly suggest that single agents are less effective than multiple herbal formulae. The basic concept of TCM consists of multiple drug therapy including rule drug, minister drug, assistant drug, and messenger drug. It is believed that herbal medications target different pathways to restore the balance of the body between Yin and Yang. This concept is quite similar to the current concept of systems pharmacology, which views therapeutic targets of drugs as parts of cellular networks that control physiological responses. Systems pharmacology aims to link genome-wide measurements and biological networks with the effects of drugs on cells, tissues, and organisms¹⁰⁶. In addition, the SDAT in TCM is an initial form of individualized treatment in modern medicine. Therefore, we believe that the modern systems biology concept might be inspired from TCM theory. However, the modern systems biology approach could be used to study the interactions among active compounds from herbal extracts in cells or tissues along with newly developed molecular biology technologies. A pioneer study in this field was published by Wang et al¹⁰⁷, in which they described the basic mechanism of Realgar-Indigo naturalis formula in treating human acute promyelocytic leukemia (APL) using systems biology and molecular biology approaches. They found that the main components of Realgar-Indigo naturalis formula are realgar, Indigo naturalis, and Salvia miltiorrhiza and their major active ingredients are tetraarsenic tetrasulfide, indirubin, and tanshinone IIA. They reported that the combination of all three ingredients yields synergy in the treatment of a murine APL model in vivo and in the induction of APL cell differentiation in vitro. This combination causes increased ubiquitination/degradation of promyelocytic leukemia-retinoic acid receptor alpha oncoprotein and enhanced G(1)/G(0) arrest in APL cells through hitting multiple targets compared with the effects of mono- or bi-agents. These data support the concept that tetraarsenic tetrasulfide serve as the principal component of the formulas, whereas indirubin and tanshinone IIA serve as adjuvant ingredients. In addition, mechanistic studies of active compounds from herbal extracts should be also performed to identify the direct drug targets and downstream signaling pathways. The role of these compounds in renal physiology and pathology should also be examined using animal models. Together, these studies could improve our understanding of the mechanism of action for individual

compounds and identify combinations of compounds that target different but complementary processes in hoped of developing a more effective therapy.

Conclusion

Therapeutic efficacy of TCHM is mainly supported by physicians' clinical experiences and small clinical studies. However, large randomized clinical trials are urgently needed to validate these therapies. Many promising therapeutic compounds could be identified from herbal decoctions and developed as anti-inflammation, anti-oxidative, or immunomodulatory pharmaceutical agents. More detailed mechanistic studies using modern scientific methodology and approaches are needed to elucidate the therapeutic potential of TCHM for CKD. Clinicians who practice TCM should be aware of the limitations of TCHM as well as their toxicity profile. The reporting system for TCHM toxicity need to be improved and pharmacologic studies are required to assess the safety profile of TCHM. The combined wisdom of modern and traditional medical physicians will be needed to develop a new strategy to assess the efficacy and the safety of traditional Chinese herbal medications in patients with CKD.

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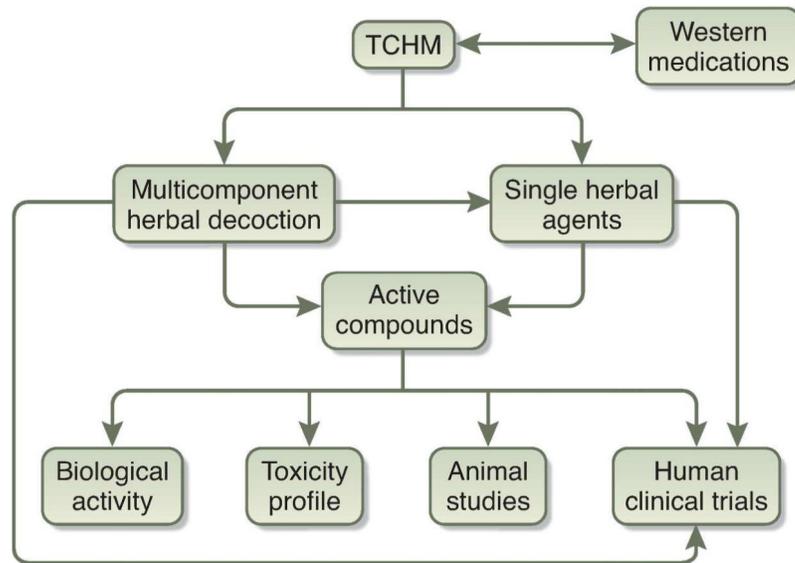


Figure 1. Schematic outlining evidence-based investigation of traditional Chinese herbal medications (TCHM)

Future studies are required to identify active compounds from TCHM, and determine their molecular mechanism of action. Well-designed animal studies and randomized clinical trials are needed to validate the physiological and pathological roles of these agents for treatment of patients with kidney disease. Complementary use of western and eastern medicines for treatment of kidney disease will also need to be further defined and proven.

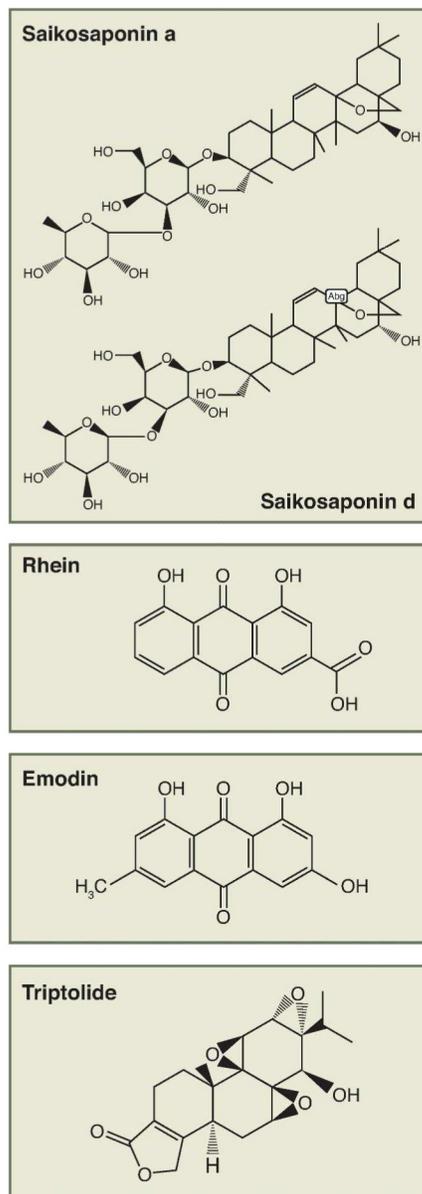


Figure 2. Chemical structures of active compounds in herbal medications used for treatment of kidney diseases in TCM

Rhein and emodin are isolated from rhubarb. Saikosaponin a (SSa) and its epimer saikosaponin d (SSd) are major triterpenoid saponin derivatives from *Radix bupleuri*.

Triptolide, a diterpene triepoxide, is one of the major active components isolated from the extracts of *Tripterygium wilfordii* Hook F.

Table 1

Comparison between Western Medicine and Traditional Chinese Medicine

	Traditional Chinese Medicine	Western Medicine
Development	Based on empirical experience of practicing TCM	Based on the scientific knowledge and practice experience.
Principles of practice	Balancing Yin-Yang and the five major elements	Understanding the molecular and cellular pathophysiology of disease and targeting therapy to normalize the underlying disease process
Disease perception	Disease is the result of interactions among different parts of the body and the environment	Disease is engendered by alterations in the cellular and molecular processes
Nomenclature of the organ	Organ system is named by the organ and its related tissues. e.g., kidney usually means the kidney and related organs such as bone, ear, etc.	Each organ has a unique name.
Diagnostic approach	Diagnosis involves inspection, auscultation and smelling, inquiry, pulse-taking and palpation*.	Diagnosis relies on history, physical examination and diagnostic testing of biological samples (pathology, blood tests, and radiographic imaging)
Principle of therapy	Apart from treatment of disease, TCM also focuses on the reaction of body to herbs. Prescription is adjusted frequently based on signs and symptoms during follow-up visits.	Emphasis is on targeted therapy that normalizes the underlying disease pathogenesis. Efficacy of treatment is evidence based. The dose of medications is adjusted or medications are changed if the effect is not achieved.
Therapy with medications	Prescription is based on the combination of multiple herbs and their interaction in order to regulate whole body system and minimize toxic effects of herbs.	Drugs are designed based on the individual target with defined molecular identify. Most patients are first treated with one drug and a second drug is added if the first medication is not efficacious.
Physician training	Based on individual experiences which are accumulated over years' practice.	Understanding of basic medical knowledge and familiarity with clinical trials and guidelines.

* inspection means observation of patient's general condition including physical appearance and activity, body movement, skin color and condition, color and appearance of the tongue, and body secretions (urine and feces). Auscultation means listening the voice, respiration, coughing, et al. Smelling means to smell the odors from patients' body, urine and feces. Inquiry is to get patients' current and past medical history. Pulse-taking is a diagnostic method performed by pressing patients' radial artery to examine the strength and variability of the pulse. Palpitation is to touch, feel, and press the skin and muscle, hand and foot, and chest and abdomen in order to detect pathological changes.

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Table 2

Summary of the mechanisms, animal studies, and human trials of the most commonly used TCHM for kidney disease (DOX-N: Doxorubicin-induced nephropathy; DN: diabetic nephropathy; UUO: unilateral ureteral obstruction; PAN: puromycin-induced nephrosis)

	Cellular mechanisms	Animal studies	Human studies
Astragalus and A&A	Regulation of immune system, diuresis, antioxidation, and anti-inflammation	Reduction of proteinuria and kidney injury in 5/6 nephrectomy, DOX-N and DN animal models. A&A exhibited an anti-fibrosis effect in PAN and UUO models	Low-to-moderate level of evidence in DN based on meta-analysis and systematic review of multiple small clinical studies
Rheum and it's components(e modin, thein)	Promotes waste product excretion through intestines and regulation of inflammation and immune response	Reduction of proteinuria and improvement in renal function and histology in 5/6 nephrectomized rats and <i>db/db</i> diabetic mice. Rheum and emodin have antioxidant effects in rat AKI models.	Low level of evidence in CKD based on meta-analysis and systematic review of multiple small and low quality clinical studies
The decoction (ST) contain Radix bupleuri and Radix bupleuri's SSa and SSd	Anti-inflammation, Immune-modulation, Anti-mesangial cell proliferative effects	ST inhibits mesangial cell proliferation in IgA and mesangio-proliferation GN models. It also decreases urinary protein excretion and kidney injury in subtotal nephrectomy model, rat model of gentamicin nephrotoxicity and mouse model of MRL/lpr. SSd reduces proteinuria and extracellular matrix deposition in mesangio-proliferative GN and DOX-N models.	Moderate level of evidence for ST in patients with IgA nephropathy, likely by inhibiting mesangial cell proliferation
Cs and it's component H1-A	Antioxidant and anti-mesangial cell proliferative effects	Cs improves renal function in animal models of ischemia/reperfusion, immunocomplex GN, MRL lpr/lpr, and 5/6 nephrectomy. Reduction of mesangial expansion in diabetic kidneys. Cs and it's component H1-A reduce hematuria and proteinuria in a murine model of IgA nephropathy.	Moderate level of evidence for Cs on cyclosporine-induced nephrotoxicity and CAN
Triptolide	Immune suppression and modulation, anti-inflammation, and anti-oxidant stress	Reduction of proteinuria and improve renal function by protecting podocyte from injury in PAN rats. Inhibition of cyst growth in PKD mice. Prevention of renal injury in murine models of DN and lupus nephritis.	Published clinical studies are only in Chinese medical journals A large clinical trial is ongoing in China