

## CHAPTER 220

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# Alternative Medicine and Chinese Herbs and the Kidney

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### OBJECTIVES

This chapter will:

1. Define complementary and alternative medicine.
2. Present general treatment principles of Chinese herbal medicine.
3. Provide an overview of mechanisms of nephrotoxicity with exposure to alternative medicine, with specific examples of herb-related nephrotoxicity.
4. Discuss possible therapeutic roles of alternative medicines in renal disease.

# DEFINITIONS

Complementary and alternative medicine (CAM) involves therapies that usually are not taught in Western medical schools. It includes a broad range of therapies and beliefs such as acupuncture, chiropractic care, relaxation techniques, massage therapy, and herbal remedies. According to the National Center for Complementary and Alternative Medicine (NCCAM) of the U.S. National Institutes of Health, *complementary and alternative medicine* is defined as a group of diverse medical and healthcare systems, practices, and products that presently are not considered to be part of conventional medicine. Although complementary medicine is usually used together with conventional medicine, whereas alternative medicine is used to replace conventional medicine, studies indicate that many patients who use alternative medicines also seek conventional treatment and vice versa. Therefore the terms “complementary” and “alternative” are used either together (complementary and alternative medicine, CAM) or interchangeably. Sometimes, the term *integrative medicine* is used to indicate the combination of mainstream medical therapies with CAM therapies that have some scientific evidence of safety and effectiveness.

Edzard Ernst commented in the *Medical Journal of Australia* that “about half the general population in developed countries use complementary and alternative medicine.”<sup>1</sup> In the United Kingdom, the annual expenditure on alternative medicine is as high as \$230 million.<sup>2</sup> CAM therapies are classified by NCCAM into five categories (Table 220.1). Traditional Chinese medicine includes acupuncture, acupressure, herbal medicine, tai chi, and qi-gong. The common characteristic of these diverse therapies is an emphasis on maximizing the body’s inherent healing ability and on treating of the “whole” person by addressing his or her physical, mental, and spiritual attributes rather than focusing on a specific pathogenic process, as is emphasized in conventional medicine.

Herbs have been used for medicinal purposes for thousands of years in the developing world. The use of botanical medicine by far accounts for the majority of

traditional remedies. Traditional medicine accounts for a substantial proportion of primary healthcare in Africa, Asia, and Latin America. In China, as much as 30% to 50% of the total medicinal consumption consists of traditional herbal preparations. Several single-center studies revealed that the consumption of traditional herbal preparations, especially Chinese traditional patent medicine, were still increasing in recent years in China.<sup>3,4</sup>

Just as with conventional drugs, all herbal products are associated with adverse reactions. Indeed, the association of alternative therapies and kidney injury is well recognized. It is beyond the scope of this chapter to present an exhaustive list of possible side effects after intake of all the different types of herbs and plants. Instead, we will highlight certain important examples and discuss the possible therapeutic roles of traditional drugs in renal disease.

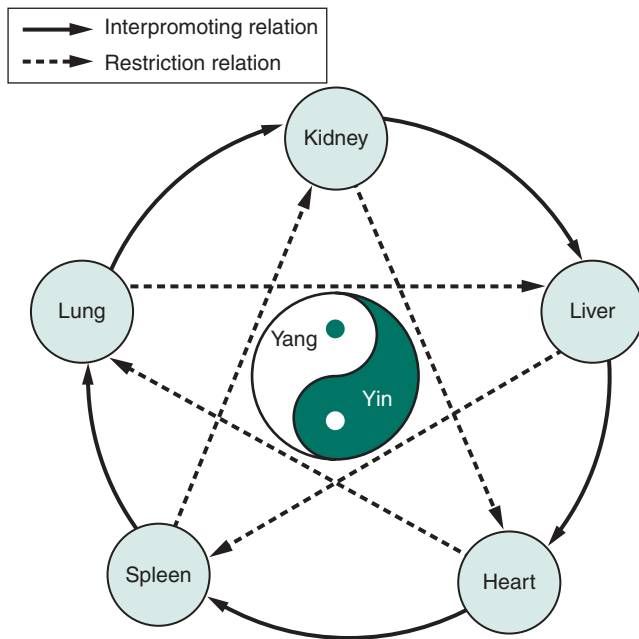
# GENERAL TREATMENT PRINCIPLES OF TRADITIONAL CHINESE MEDICINE

The concept of disease in Chinese medicine is different from that of conventional Western medicine. Disease is regarded as an imbalance between the health, *qi*, and pathogenic factors. This *qi* runs within the vessels and has a nutritive action. Sickness is also a result of *yin-yang* disharmony between different parts of the body (*zang-fu*, internal organs) and in the whole body (Fig. 220.1, Table 220.2). Therefore the primary therapeutic principle of Chinese medicine is to strengthen the health *qi*, eliminate the pathogenic factors, and restore the *yin-yang* harmony of the body parts as well as with the environment. On the whole, Chinese medicine takes on a more holistic approach besides the use of herbs. Treatment targeting the kidney may not consist of treating illness arising from kidney dysfunction. Diarrhea can be stopped by herbs that “warm” the kidney with *yang* deficiency. Sexual impotence also can be treated by “warming” the kidney to revitalize *yang*. On the other hand, diuresis can be induced by warming the kidney with some other herbs in relieving edema caused by kidney *yang* deficiency.

**TABLE 220.1**

**Classification of Complementary and Alternative Medicine**

CATEGORY	DESCRIPTION	EXAMPLES
Alternative medical systems	Built on complete systems of theory and practice	Traditional Chinese medicine Ayurveda Homeopathic medicine Naturopathic medicine
Mind-body interventions	Designed to enhance the mind’s capacity to affect bodily function and symptoms	Meditation Prayer Mental healing Art therapy Music therapy
Biologically based therapies	Use substances found in nature	Vitamin or dietary supplements Natural products (e.g., shark cartilage and <i>Ling Zhi</i> to treat cancer)
Manipulative and body-based methods	Involve body manipulation and/or movement of one or more parts of the body	Chiropractic/osteopathic manipulation Body massage
Energy therapies	Involve use of energy fields	Qi-gong Reiki Therapeutic touch



**FIGURE 220.1** Explanation of pathogenesis in traditional Chinese medicine.

**TABLE 220.2**

**Clinical Manifestation of yin-yang Disharmony**

YANG DEFICIENCY	YANG EXCESS
Hypoactivity	Hyperactivity
Chronic disease/gradual onset	Acute disease/rapid onset
Slowly changing symptoms	Rapid pathologic changes
Quiet, lethargy, sleepiness	Restlessness, insomnia
Wants to be covered	Throws off bedclothes
Lies curled up	Lies stretched out
Cold limbs and body	Hot limbs and body
Pale face	Red face
Weak voice, no desire to talk	Loud voice, talkative
Shallow, weak breathing	Coarse breathing
No thirst/wants warm drinks	Thirst esp. for cold drinks
Copious, clear urine	Scanty, dark urine
Loose stools (fluids not transformed)	Constipation (damage to fluids by heat)
Clear, copious secretions	Thick, sticky white/yellow secretions
Excessive moisture	Excessive dryness (throat, skin, eyes, etc.)
Degenerative disease	Inflammatory disease
Pale tongue, white coat	Red tongue, yellow coat
Empty pulse	Full pulse

## MECHANISMS OF NEPHROTOXICITY OF HERBAL MEDICINE

The kidney is responsible for the excretion of chemicals and drugs. The high blood flow rate, large endothelial surface area, active uptake by tubular cells, and medullary concentration of toxins make the kidney vulnerable to the toxicity of drugs. A toxin may achieve a very high concentration in the renal tubules because of their concentrating capabilities. Herbal and plant products are among the most frequent

causes of acute kidney injury (AKI) in Africa.<sup>5</sup> Traditional herbal preparations are also important causes of AKI in China.<sup>6,7</sup>

Herbal pharmacopoeias usually include active and useful compounds as well as toxic substances. The relative paucity of professional surveillance, the lack of industrial standardization, and the often-undisclosed secret formulas pose significant hazards to consumers.<sup>8–11</sup> Furthermore, commercial plant products may lack purity or potency because of variability in the amount of ingredients.<sup>12</sup> Herbal medicine may be the source of kidney injury via a number of mechanisms:

1. Known herb with unknown or underestimated toxicity
  2. Toxic effect related to wrong preparation or use of substitute
  3. Contaminants or adulteration
  4. Indirect toxicity related to drug-drug interaction
- They may result in a variety of clinical manifestations and/or pathologic changes in the kidney (Table 220.3).

## HERBS WITH KNOWN TOXICITY

### Herbs Containing Aristolochic Acid

Aristolochic acid (AA) is derived from an extract of plants such as *Aristolochia fangchi*, *Radix et Rhizoma Asari*, *Aristolochia manshuriensis*, *Aristolochia cucurbitifolia*, *Aristolochia debilis*, and *Aristolochia contorta*. Herbs containing AA have been widely used. However, there are increasing reports on renal toxicity and carcinogenicity of AA.

Aristolochic acid nephropathy (AAN) is characterized by tubulointerstitial injury, including mild tubular proteinuria, anemia, and initially normal blood pressure in approximately one half of patients. Human subjects with high AA intake may progress to kidney failure 1 to 7 years later, although subjects with low cumulative AA intake usually can keep relatively normal renal function over the 2 to 8 years follow-up. AAN has been classified as a separate entity of progressive tubulointerstitial nephropathy. The major pathologic findings of AAN include hypocellular interstitial fibrosis, tubular atrophy, tubular brush border ablation, fibromyxoid or fibrous intimal thickening mainly of the interlobular arteries, mild to severe hyalinization, and sclerosis of the glomeruli decreasing from the outer to the inner cortex.<sup>13</sup>

Urothelial malignancy is observed mainly in the upper urinary tract, such as the ureter and pelvis, during the first 3 years after exposure but also can be observed in the bladder, with an approximately equal tendency, after longer follow-up periods.<sup>13,14</sup>

### Licorice (*Glycyrrhiza glabra*)

Licorice roots contain 5% to 9% glycyrrhizic acid, a glycoside that is much sweeter than sugar. Derivatives from licorice can be used to treat peptic ulcer disease.

Aqueous extracts of licorice contain 10% to 20% glycyrrhizic acid. Glycyrrhizic acid is hydrolyzed by intestinal flora to glycyrrhetic acid, which inhibits 11 $\beta$ -hydroxysteroid dehydrogenase in the kidney. This enzyme catalyzes inactivation of cortisol; therefore the use of licorice may result in a state of pseudohyperaldosteronism.<sup>9,10</sup> Toxicity may manifest as headache, sodium and water retention, hypokalemia, heart failure, and even cardiac arrest.

TABLE 220.3

## Kidney Syndromes Associated with the Use of Alternative Medicines

Acute tubular necrosis	Traditional African medicine: toxic plants ( <i>Securidaca longepedunculata</i> , <i>Euphorbia matabalensis</i> , <i>Crotalaria laburnifolia</i> , <i>Heliotropium</i> , <i>Symphytum</i> , <i>Senecio</i> plants, <i>Callilepis laureola</i> , <i>Atractylis gummifera</i> , Cape Aloes) or adulteration by dichromates Sri Lankan traditional Ayurvedic pharmacopoeia: toxic plants ( <i>Crotalaria</i> spp., <i>Cassia auriculata</i> , <i>Holarrhena antidysenterica</i> ) Asian rural areas: raw carp bile Saudi Arabia: raw sheep bile China: <i>Taxus celebica</i> Hydrazine sulfate <i>Mentha spicata</i> Chinese herbs contaminated with arsenic ( <i>Niu Huang Chieh tu Pien</i> ) Morocco: <i>Takaout roumia</i> (PPD) Sudan: henna adulterated with PPD Cantharidin Chelation therapy with EDTA <i>Glycyrrhiza</i> spp. (herbal cough mixtures, Chinese herbal teas, gancao, Boui-ougi-tou) Chinese herbs contaminated with cadmium Germanium
Proximal tubulopathy (Fanconi syndrome)	Traditional African medicine: toxic plants (Cape Aloes)
Distal tubular toxicity	Peruvian medicine ( <i>Uno degatta</i> )
Acute interstitial nephritis	China: <i>Taxus celebica</i> Chinese herbs adulterated with NSAIDs ( <i>Tung Shueh</i> pills) <i>Hypericum</i> , <i>Iedum</i> <i>Dioscorea quinqueloba</i>
Analgesic nephropathy, papillary necrosis	Willow bark ( <i>Salix</i> spp.) Chinese herbs adulterated with NSAIDs (indomethacin, diclofenac, mefenamic acid, phenylbutazone): <i>Chuifong Tuokuwan</i> , <i>Tung Shueh</i> pills, others
Hypertension	<i>Glycyrrhiza</i> spp. (herbal cough mixtures, Chinese herbal teas, gancao, Boui-ougi-tou) Ephedra-containing herbal preparations ( <i>Ma Huang</i> , dietary supplements containing ephedra alkaloids)
Kidney stones	Ephedra-containing herbal preparations ( <i>Ma Huang</i> , dietary supplements containing ephedra alkaloids) Cranberry juice (oxalate) Chinese herbs contaminated with cadmium
Urinary retention	Niger: <i>Datura</i> spp. ( <i>Sobi-lobi</i> ) Chinese herbs: <i>Rhododendron molle</i> , <i>Rehmannia glutinosa</i> , <i>Carthamus tinctorius</i> , <i>Atropa belladonna</i> , <i>Hyoscyamus niger</i> , <i>Datura</i> spp.
Chronic tubulointerstitial nephritis with fibrosis	Chinese herbs containing <i>Aristolochia</i> sp.: Belgian slimming regimen, Mokutsu, Boui
Urinary tract carcinoma	China: <i>Jia Wey Guo Sao</i> pills (herbal mixtures without <i>Aristolochia</i> )
Acute rejection of kidney transplant	Chinese herbs containing <i>Aristolochia</i> sp.: Belgian slimming regimen Drug interaction with alternative medicine: St. John's wort Immunostimulating drugs: alfalfa ( <i>Medicago sativa</i> )

EDTA, Ethylenediamine tetra-acetic acid; NSAIDs, nonsteroidal antiinflammatory drugs; PPD, paraphenylenediamine.

From Colson CR, De Broe ME: Kidney injury from alternative medicines. *Adv Chronic Kidney Dis* 2005;12:261–275.

Glycyrrhizic acid is mainly used as a flavoring and sweetening agent for bitter drugs, beverages, candies, and chewing gum. It also may be present in some cough and cold mixtures. Many health products and Chinese herbal teas contain considerable amounts of glycyrrhizic acid. Excessive intake of these products may result in Fanconi syndrome.<sup>15–17</sup>

## Ma Huang

*Ma Huang* is a Chinese herbal preparation that contains ephedra. The vasoconstrictive effects of ephedra (primarily from ephedrine and pseudoephedrine) render it useful in conditions characterized by edematous tissues and congested membranes. Although it is used to treat patients with respiratory symptoms and common cold, it also is in widespread use as a weight loss aid (appetite suppressant) and euphoria agent (for its central nervous system stimulant properties). The most common toxic effects are usually those resulting from its sympathomimetic activity, such as hypertension, palpitation, tachycardia, and stroke.<sup>9</sup> It may cause damage to the kidney secondary to ephedrine nephrolithiasis.<sup>9,18</sup>

## Flavonoid Drugs

Flavonoids are plant constituents that are used in Europe to treat disorders of the peripheral circulation, liver diseases, phalloides intoxication, and intolerance to radiation therapy. They have been used widely around the world for many years. In China, extracts of *Taxus celebica*, which contains sciadopitysin, a flavonoid compound, are used in traditional medicine to treat diabetes mellitus.<sup>10</sup>

Intoxication manifests with fever and gastrointestinal upset several hours after taking a large dose of a flavonoid compound. This is followed by oliguric renal failure, cola-colored urine, and jaundice. Patients may develop hemolysis, cholestatic hepatitis, and disseminated intravascular coagulopathy. Biopsy shows acute interstitial nephritis with acute tubular necrosis.<sup>19</sup> The exact mechanism of flavonoid-induced renal failure is unknown. Acute tubulointerstitial nephritis and tubular necrosis could be the result of tubular toxicity of hemoglobin from intravascular hemolysis. Direct nephrotoxicity through accumulation and uptake into tubular cells may be responsible and may explain why some patients develop renal failure after taking flavonoids for a prolonged period.

## USE OF WRONG PREPARATION OR SUBSTITUTE

Plants may look alike and may even be considered to be interchangeable in certain traditional remedies. Furthermore, plants may get mixed up because they have similar names. A well-known example occurred in Brussels, Belgium, and involved the use of incorrectly identified herbs in slimming pills. In 1992 there was an outbreak of severe nephritis among young women in Brussels. Epidemiologic survey identified a total of nine cases of renal failure among women who had undergone a slimming regimen in the same medical clinic.<sup>20</sup> Biopsy of the kidneys revealed extensive interstitial fibrosis, whereas the glomeruli were relatively spared. Patients progressed rapidly to end-stage renal failure (ESRF). Retrospectively, it was found that the clinic had changed the weight reduction regimen and introduced powdered extracts of Chinese herbs in the slimming pills. Subsequently, the syndrome was named Chinese herb nephropathy (CHN). Further investigation suggested that one of the herbs in the formula, *Stephania tetrandra*, was replaced by *Aristolochia* species because of misidentification.<sup>20,21</sup>

After publication of the index cases, similar cases were reported all around the world.<sup>22–24</sup> As a result of this episode, AA (*Aristolochia* spp.) is probably the most notorious and best studied nephrotoxic herb-related agent. The major histologic finding of the renal biopsy from affected kidneys is interstitial fibrosis with relative sparing of glomeruli.<sup>25</sup> AAN is characterized by a lower proteinuria, more severe anemia, and faster progression to renal failure than other interstitial nephropathies.<sup>22</sup> Many patients developed ESRF and required maintenance dialysis or renal grafting. In Japan, AA was reported to be associated with Fanconi syndrome.<sup>10</sup> Proximal tubular cells were probably the primary target in this nephropathy.<sup>9</sup>

Exposure to AA also is associated with a high incidence of uroepithelial tumorigenesis.<sup>9,26</sup> Attention was drawn to carcinogenicity after the discovery of cellular atypia throughout the urothelium of native kidneys removed at the time of transplantation in three patients with AAN. Subsequently, in another 39 patients with AAN who were being treated with dialysis or underwent transplantation, prophylactic surgical removal of native kidneys and ureters was performed. Among them, 18 cases of urothelial carcinoma were found, and mild-to-moderate dysplasia was found in 19 of the 21 remaining patients.<sup>26</sup> Regular cystoscopy therefore was recommended for patients with AAN.

## CONTAMINANTS AND ADULTERANTS

Impurities or the unexpected presence of chemicals or medication in alternative formulas is no rare finding.

### Heavy Metals

Heavy metals may be introduced during manufacturing or by natural means because of the ubiquitous problem of soil and water pollution in certain regions. High levels of lead and cadmium have been found in some herbal medicines.<sup>27</sup> Furthermore, minerals or other adulterants may be added to traditional medicines for therapeutic purposes. Cadmium, lead, mercury, and arsenic have been identified in this context.<sup>10,21</sup> Details of nephrotoxicity resulting from

heavy metal ingestion can be found in textbooks related to poisoning and drug overdose.<sup>28</sup>

Other nephrotoxic contaminants that have been identified in various reports include mefenamic acid, ephedrine, phenylbutazone, and paraphenylenediamine (PPD).<sup>9,10,29</sup> They have been found in the Chinese herbal mixtures (*Chufong tuokuwan*), Chinese herbal pills (*Tung Shueh*), and some other herbal preparations for arthralgia. Their presence has resulted in various types of renal injury, including interstitial nephritis, bilateral papillary necrosis, and kidney failure.

## DRUG INTERACTIONS

One of the problems of the use of alternative medicine is multipharmacy. Many patients take herbs as supplementary medicine in addition to whatever they have been prescribed. This is especially alarming in patients with underlying renal disease and in those who have undergone transplantation, who are usually taking multiple conventional medications.

St. John's wort (*Hypericum perforatum*) is promoted as an antidepressant and anxiolytic agent. The active constituents are believed to be hypericins or hyperforins.<sup>11,30</sup> The proposed mechanism of action lies in the inhibition of serotonin, dopamine, and norepinephrine reuptake in the central nervous system. A number of systemic reviews and randomized trials have supported the efficacy of St. John's wort in patients with depression.<sup>11,31</sup> Although St. John's wort has a good safety profile as monotherapy,<sup>31</sup> concerns have been raised with regard to the possibility of important drug interactions.<sup>32,33</sup> Coadministration of St. John's wort reduces the plasma levels or efficacy of various conventional medicines. Induction of the cytochrome P-450 isoenzyme CYP3A4 and P-glycoprotein has been proposed as the underlying mechanism.<sup>11</sup> There are reports of acute graft rejection after renal transplantation, presumably because of decreased cyclosporine or tacrolimus activities after taking St. John's wort.<sup>34,35</sup>

## OTHER ALTERNATIVE THERAPIES

Other alternative therapies also may be associated with renal injury.

### Body Massage

Body massage is a type of CAM used to relieve pain or improve quality of life. It is considered relatively safe. However, recently there was a report of acute renal failure secondary to body massage. Rhabdomyolysis was induced by too vigorous body massage in an elderly man with diabetes mellitus.<sup>36</sup> Inadequate water intake potentiating the effect of rhabdomyolysis was postulated.

### Mesotherapy

Mesotherapy is a form of CAM that involves multiple microinjections of homeopathic medication into mesoderm. It is used as a form of treatment for osteoarticular disease and recently has been used also as part of slimming regimens and cosmetic procedures. A case of ESRF resulting from rapidly progressive interstitial fibrosis after mesotherapy has been reported. An advanced degree of tubular loss and



atrophy with tubulointerstitial fibrosis and progression to ESRF was observed. Inadvertent use of nephrotoxin for injection was suspected.<sup>37</sup>

therapy mixture<sup>39</sup> purchased via the Internet were reported. A thorough history of chemicals or drugs taken is imperative in any patients suffering from renal injury.

### Chelation Therapy

Chelation therapy is a process involving use of chelating agents to remove heavy metals from the body. It is a form of therapy with application in conventional as well as alternative medicine. Ethylenediaminetetraacetic acid (EDTA) chelation therapy is used as a form of alternative therapy for atherosclerotic heart disease. Its effect is achieved by improving metabolic function and blood flow through blocked arteries throughout the body. This form of therapy has been reported to be associated with acute renal failure due to acute tubular necrosis.<sup>37</sup> The mechanism of nephrotoxicity is unknown, but release of heavy metals with subsequent deposition in the tubulointerstitium may be the cause. Patients with preexisting renal disease are more prone to the risk of nephrotoxicity.

Easy access to multiple chemicals or alternative medical agents via the Internet contributes to the diversity of kidney injury. For example, cases of renal failure after use of an alternative cancer remedy<sup>38</sup> and ingestion of an aromatic

### THERAPEUTIC ROLES OF ALTERNATIVE THERAPIES IN KIDNEY DISEASE

Herbal medicine does not necessarily lead to nephrotoxicity. More than 50% of drugs used in the Western pharmacopoeia owe their origin to herbs and chemicals derived from plants.<sup>9,40</sup> Herbs may be of benefit to kidney health. Many herbs have been employed for their diuretic and renal protective actions for centuries. Studies are ongoing with regard to the use of herbs as treatment for kidney disease (Table 220.4).

#### *Cordyceps sinensis*

*Cordyceps sinensis* (Cs) is a blade-shaped fungus that derives its nutrients from the larvae of *Lepidoptera* spp. found at high altitudes. In Chinese medicine, Cs is used as a kidney

**TABLE 220.4**

**Summary of the Mechanisms of the Most Commonly Used Herbs for Kidney Disease**

HERBAL NAME	MAIN ACTIVE COMPOUNDS	MECHANISMS	ANIMAL STUDIES	HUMAN STUDIES
Astragalus	Astragalosides I-VII, flavonoids, etc.	Regulation of immune system, diuresis, antioxidation, and antiinflammation	Reduction of proteinuria and kidney injury in 5/6 nephrectomy, DOX-N and DN animal models. A&A exhibited and antifibrosis effect in PAN and UUO models	Low to moderate level of evidence in DN based on meta-analysis and systemic review of multiple small clinical studies
Rhubarb	Emodin and rhein	Promotes waste product excretion	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.
Radix bupleuri	Saikosaponin a & d	Antiinflammation, immune-modulation, antimesangial cell proliferative effects	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 (decoction contains Radix bupleuri) in patients with IgA nephropathy, likely by inhibiting mesangial cell proliferation
Cordyceps sinensis (Cs)	H1-A	Antioxidant and antimesangial 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 kidney disease. Cs and its 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
Tripterygium	Triptolide	Immune suppression and modulation, antiinflammation, and antioxidant stress	Reduction of proteinuria and improvement in renal function by protecting podocyte from injury in PAN rats. Inhibition of cyst growth in PKD mouse. 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.

DN, Diabetic nephropathy; DOX-N, doxorubicin-induced nephropathy; UUO, unilateral ureteral obstruction; PAN, puromycin-induced nephrosis. From Zhong Yf, Deng YY, Chen YP, et al. Therapeutic use of traditional Chinese herbal medications for chronic kidney diseases. *Kidney Int.* 2013;84:1108–1118.

tonic. In vitro studies demonstrated antioxidant activity and inhibition of mesangial cell proliferation.<sup>40</sup> Several studies in Chinese medical literature have reported that Cs could improve renal function in CKD and AKI patients.<sup>41</sup> However, more clinical studies are needed to evaluate fully the role and toxicity of this traditional and valued medication from ancient China.<sup>42</sup>

## Astragalus

The medicinal herb Astragalus is derived from the root of Leguminosae plant *Astragalus membranaceus* or *Astragalus mongholicus*. Astragalus is used in many Chinese recipes for renal disorders, and a diuretic effect has been observed.<sup>40</sup> Pharmacologic studies have shown that several compounds from Astragalus have multiple effects including stimulating the immune system, diuresis, antioxidation, and antiinflammation. In addition, *A. membranaceus* has been shown to attenuate podocyte injury induced by complement membranous attack complex.<sup>41</sup> As an adjunctive treatment to conventional therapies, Astragalus was found to offer some promising effects in reducing proteinuria and increasing hemoglobin and serum albumin.<sup>43</sup>

## Tripterygium

Extracts of *Tripterygium wilfordii* Hook F have been used to treat glomerulonephritis for more than 30 years in China with remarkable antiproteinuric effect. Triptolide, a diterpene triepoxide, is one of the major active components of these extracts. Triptolide has potent immunosuppressive, immunomodulatory, and antiinflammatory effects. Tripterygium preparations may have nephroprotective effects, but high-quality trials are required to reliably determine the balance of benefits and harms.<sup>41,43</sup>

## Rhubarb

The medicinal herb rhubarb is derived from the root of the *Rheum palmatum* L plant. It is a strong cathartic and is thought to increase the excretion of waste products, including nitrogenous waste accumulated in patients with renal failure, through the intestines. Hence, rhubarb has been used to treat patients with renal failure. Recently, studies suggest that emodin and rhein, two major active components of rhubarb, play roles in the regulation of inflammation and immune response.<sup>43</sup> In animal studies, it decreases proteinuria and glomerulosclerosis.<sup>44</sup> Clinical studies also suggested that rhubarb was able to reduce proteinuria and improve renal function individually and may cause further reduction of proteinuria and improvement of renal function when used together with angiotensin converting enzyme inhibitors (ACEIs).<sup>43</sup>

## Radix bupleuri

*Radix bupleuri* is a major component of the Chinese recipe Saireito. Saireito has been used widely in China

and Japan for treatment of kidney diseases. In animal studies, Saireito prevented mesangial cell proliferation and reduced proteinuria. Clinical studies also suggested that Saireito could reduce urinary protein excretion and hematuria.<sup>41</sup>

## Others

*Salvia miltiorrhiza* root contains many phenolic compounds with strong antioxidant actions. It is used in Chinese traditional formulas for renal failure. Ginsenoside-Rd demonstrated a renal protective effect in animal models.<sup>45,46</sup>

On the whole, the risk-benefit profile and the efficacy of herbal remedies are matters of concern. Further experiments are necessary to determine the roles of these medicines in the treatment of renal disease.

### Key Points

1. CAM is used widely all over the world.
2. Herbs are the most common example of CAM.
3. CAM-induced renal injury may be due to known drugs with nephrotoxicity, wrong constituents, contaminants and adulterants, or drug interactions.
4. Aristolochic acid is believed to be the agent responsible for Chinese herb nephropathy. Licorice, *Ma Huang*, St. John's wort, heavy metals, and flavonoids can cause renal damage.
5. Therapeutic values of many herbs for renal disease are still under study.
6. Today's easy access to various chemicals and remedies with acclaimed therapeutic values results in increasing numbers and varieties of renal intoxication.
7. Enquiry regarding the use of CAM should be included in the patient history and assessment of renal failure.

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