

CHAPTER

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Herbal Drugs and Acute Renal Injury

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There always has been a belief about allopathic medicines that they are more toxic and have greater side-effects than medicines from other branches of sciences viz. Homeopathy, Unani, etc. The science of 'Ayurveda' and its medicines exist in India since time immemorial. The name of Dhanvantri vaidya is enshrined in the mythology and in ancient scriptures also one finds the mention of use of liniments, tamra leaves and turmeric on wounds and injuries. The Government of India has supported and opened ventures in the field of complementary and alternative medicine (CAM) in the last one decade or so, which is a welcome move, since it will promote research and standardisation of medications used in CAM. However, as has always been the practice, there are a number of persons in the society who are unqualified and/or incompetent to prescribe medicines in any branch of medicine whether it be allopathy or homeopathy or branches from CAM, but these faith-healers and quacks are inherently mingled with the society and prescribe medicines injudiciously causing more damage than good. In fact, recent studies have suggested that there has been a rise in usage of alternative therapies not only in the developing countries but also in the developed world and a significant number of these could be herbal medicines. An oft quoted survey of alternative medicine revealed that 42% Americans used alternative therapies

with 12% of these therapies being use of herbal supplements. Moreover, over two-thirds of people using alternative therapies did not report this piece of information to their health care providers¹. In fact, 75% of world population depend on botanical medicines for their basic health care needs and over 50% of drugs in Western pharmacopoeia are isolated from herbs². These herbal medicines and dietary supplements could be unstandardised or unresearched, lacking consistent requirements for rigorous safety, efficacy and purity testing resulting in varying amounts of active constituents from batch to batch; and thus may cause irreparable damage to the unsuspecting patients. This lack of consistency in composition and biologic activity is coupled with problems in plant identification, variable growing conditions, differences in processing extracts and lack of information about pharmacologically active compounds.² In spite of this, the use of herbal medicines continues to grow in many disease conditions, but the risk from use may overshadow potential benefit, especially in vulnerable patients who may be in a compensated state and require minimal insult to their jeopardised systems to trip over in to a decompensated disease. Renal compromised patients constitute one such group. Even patients harboring significant co-morbidities viz. diabetes, hypertension or coronary artery disease may be at an increased risk to develop

kidney disease as a result of these unsolicited medicines. Renal patients are also more likely to seek such therapies, because of the chronic nature of their illness, high financial cost of the medicines, disenchantment with available renal replacement therapies and adverse side effects or lack of efficacy from conventional medicines. In the ensuing article, one will find herbs which are associated with renal injury in the acute or chronic setting in the healthy individuals and in kidney-disease individuals.

A number of anatomical, physiological and biochemical features attributable to the kidney make it particularly sensitive to injury as a result of exposure to exogenous compounds viz. herbal agents. These include a large blood flow, high endothelial surface area, high metabolic activity, active uptake by tubular cells and medullary interstitial concentration, presence of a variety of xenobiotic transporters and metabolising enzymes, and concentration of solutes during urine production. Besides, the conjugation of exogenous agents to glutathione and/or cysteine targets these chemicals to the kidney where inhibition of renal function occurs through varied mechanisms. Agents like aristolochic acids can affect the renal cytochrome P450 metabolism and induce renal injury. The toxins may injure the tubules directly, at the site of toxin transport or concentration, or by inducing renal ischemia, hemoglobinuria or myoglobinuria.^{3,4} Continued exposure and exposure to high doses can increase the severity of renal failure. Of the several lesions that have been described after nephrotoxic injury, acute tubular or cortical necrosis and acute interstitial nephritis is the most frequently encountered. However, other renal syndromes that have been associated with herbal drugs include Fanconi's syndrome, hypokalemia, hypertension, papillary necrosis, chronic interstitial nephritis, nephrolithiasis, urinary retention and carcinoma of the urinary tract².

Various herbal agents that are known to be toxic can be classified⁵ into

1. Agents which are directly nephrotoxic,

2. Herbal drugs which result in electrolyte abnormalities by acting upon the kidney,
3. Agents which can predispose to formation of stones (oxalate stones),
4. Agents which act as diuretics,
5. Herbal drugs which contain heavy metals or other drugs and
6. Herbal agents which can interact with other drugs especially in the renal transplanted subject.

Herbs which are directly nephrotoxic

1. **Chinese herb nephropathy or Aristolochic acid nephropathy**⁶⁻¹⁰- In Belgium between 1990-1992, nephrotoxicity was reported in over 100 persons consuming a Chinese weight loss herbal remedy containing aristolochic acid; and 70 of these required renal transplants or dialysis and 30 subsequently developed urothelial carcinoma. In fact, May 1990 witnessed a change in slimming therapy incorporating two Chinese herbs namely *Stephania tetrandra* and *Magnolia officinalis*. A specific type of fibrosing interstitial nephritis was observed with their usage.¹⁰ Aristolochic acid is a nitrophenanthrene carboxylic acid which forms DNA adducts in renal as well as other tissues after metabolic activation. The DNA adducts result in genotoxic mutations resulting in urothelial carcinoma as well as the characteristic renal interstitial fibrosis and extensive loss of cortical tubules. Several other plants particularly from the *Asarum* and *Bragantia* genera, contain aristolochic acid. Patients present with renal insufficiency, moderate increase in blood urea, mild proteinuria, severe anemia and urinary sediment. Glycosuria and sterile proteinuria are common and usually indicate tubular dysfunction. Disease usually progresses rapidly to end stage renal disease. No therapy has been found to be effective, although a beneficial effect with steroids has been suggested.¹¹ Renal transplant is effective in patients who progress to end-stage renal

disease and no recurrence has been reported in transplanted kidney.

2. **Balkan endemic nephropathy** has been reported from the Balkan states, resulting from plant products contaminated by the fungal mycotoxin ochratoxin A, which also forms mutagenic DNA adducts in kidney tissue. However, the exact etiology of Balkan endemic nephropathy is still a mystery.¹²
3. **Djenkol bean poisoning (Djenkolism)**¹³⁻¹⁵ is a cause of acute renal failure occurring in the tropics. Symptoms of poisoning occur soon after or up to 36 hours of ingestion. Symptoms include fever, leukocytosis, lower abdominal and bilateral lumbar pain, dysuria, hematuria, oligo-anuria, passage of sandy particles in the urine and hypertension; manifesting as acute renal failure. High fluid intake and urinary alkalinisation with sodium bicarbonate helps in dissolving crystals; and majority of patients recover within a few days. Djenkol bean is a pungent smelling edible fruit of the hardwood tree *Pithecellobium labatum* (Jering trees). These may be eaten raw, fried or roasted and contain djenkolic acid, a sulfur rich cysteine thioacetal of formaldehyde. Djenkolic acid produces severe tubular necrosis with a lesser degree of glomerular cell necrosis in animals. Djenkolic acid forms needle like crystals, specially in concentrated acidic urine in distal tubules, leading to obstruction, which acts as a nidus for stone formation.
4. **Impila poisoning**- It is a herb derived from the tuberous roots of the plant *Callilepis laureola*, and is used as a traditional remedy in South Africa to treat a number of conditions; often given during pregnancy to ensure easy childbirth, for sexually transmitted diseases for fertility and blood purification. It has marked hepatic and renal toxicity. In fact, it is one of the most common causes of ARF in black population of South Africa.¹⁶ Symptoms appear in 1-4 days in > 70% cases manifesting as nausea and

vomitings followed by hypoglycemia leading to altered sensorium and convulsions. Patient has oliguric renal failure, oliguric phase lasting 8-12 days and serum creatinine rises 0.5-1.0 mg/day. Treatment is largely supportive, but the mortality is high (> 50%). Renal damage caused is characterised by acute proximal convoluted tubule and loop of Henle necrosis resulting in renal failure.

5. **Mushroom poisoning**- Ingestion of wild mushrooms containing the nephrotoxin orellanine has resulted in acute renal failure.¹⁷ Kidney biopsy showed marked tubular interstitial nephritis and fibrosis.
6. **Cat's claw (*Uncaria tomentosa*)**- It is a Peruvian herbal preparation used for gastritis, rheumatism, cirrhosis, gonorrhoea and cancers of the female genital tract and has been associated with development of acute renal failure; kidney biopsy showing acute interstitial nephritis.

Herbal drugs that can alter serum potassium levels

1. **Licorice root (*Glycyrrhiza glabra*)**- in high doses and when used for long durations causes aldosterone like effect resulting in sodium retention and consequent hypertension and hypokalemia. Licorice root contains glycyrrhizic acid which is hydrolysed to glycyrrhetic acid which in turn inhibits renal 11-hydroxysteroid dehydrogenase thus preventing inactivation of cortisol to cortisone. Accumulation of cortisol in the kidney stimulates aldosterone receptors in cells of cortical collecting duct resulting in sodium reabsorption.
2. **Laxative herbs**- Senna (*Senna Alexandria*) and rhubarb (*Rheum officinale*) which are used as laxatives can result in electrolyte imbalance particularly hypokalemia.
3. **Noni juice (*Morinda citrifolia*)** derived from the noni fruit is a popular herbal supplement which is also available in India and is used for its immune-boosting properties in many diseases

and in convalescence and rehabilitation. However, it can result in serious hyperkalemia due to its high content of potassium (56.3 meq/L), which is similar to orange and tomato juices.¹⁸

4. **Dandelion (*Taraxacum officinale*)**, stinging nettle (*Urtica dioica*), horsetail (*Equisetum arvense*), and alfalfa (*Medicago sativa*) are other popular herbs which can also contribute to hyperkalemia.

Herbal drugs that have high content of oxalic acid

1. **Rhubarb (*Rheum officinale*)**- It is a common herbal preparation but has high oxalate content and can promote the formation of renal calculi.
2. **Star fruit (*Averrhoa carambola*)**- ingestion has been reported to produce acute oxalate nephropathy.¹⁹

Herbal drugs with diuretic activity

1. Juniper berry (*Juniperus communis*), parsley (*Petroselinum crispum*), dandelion (*Taraxacum officinale*), horsetail (*Equisetum arvense*), asparagus root (*Asparagus officinalis*), lovage root (*Levisticum officinale*), goldenrod (*Solidago virgaurea*), uva ursi (*Arctostaphylos uva ursi*), stinging nettle leaf (*Urtica dioica*), and alfalfa (*Medicago sativa*) have been traditionally used as diuretics in health and disease. These herbs have varying degrees of diuretic activity and their use requires caution in healthy individuals as well as in the renal-compromised patient. Some of these herbs act as irritants to the tubular cell while some may alter serum electrolytes. Juniper berries contain terpine-4-ol which may cause kidney irritation and damage in excess. In Germany, parsley and goldenrod are indicated for systemic irrigation of the urinary tract and for preventing kidney stones. The diuretic effect of parsley leaf and root is due to its volatile oil components myristicin and apiol. Also

in Germany, dandelion, horsetail, and uva ursi are licensed as standard medicinal teas to stimulate diuresis.

Herbal products containing heavy metals

It is a widely known fact and well-corroborated that many herbal medications particularly Chinese and Ayurvedic herbal preparations contain nephrotoxic heavy metals viz. lead, mercury, cadmium and arsenic². Firstly many heavy metals are considered to have therapeutic effects in the CAM specialities. Secondly, the problem lies in the fact that their concentration is not standardised and there is great batch to batch variability. Thirdly, the presence of heavy metals and their concentrations are many a times not revealed on the labels of herbal medicines.

Herbal drugs containing other drugs

It has been recognised that many herbal formulations contain non-steroidal anti-inflammatory drugs which inhibit renal vasodilator prostaglandins and can lead to renal failure.

Other drugs that have been reported to be present in herbal medications include ephedrine, steroids, fenfluramine, methyltestosterone, phenacetin and sildenafil².

Herbal drugs with immunomodulating properties (in the renal transplant patient)

1. ***Echinacea (Echinacea purpurea)***- is a herbal remedy which is promoted as an immune system stimulant. Ingestion of this drug could seriously jeopardise the transplanted kidney of the patient taking immunosuppressant drugs.
2. ***St. John's wort (Hypericum perforatum)***- causes a decrease in serum cyclosporine levels and again can compromise a successful organ transplant.

The National Kidney Foundation (NKF) of the USA has prescribed guidelines under the head-

Table 1 : Herbs implicated in causing renal injury

Herbs known to be unsafe for all people	Herbs that may be toxic to the kidneys	Herbs that may be harmful in chronic kidney disease
Chapparal, Pennyroyal, Comfrey, Pokeroot, Ephedra (Ma Huang), Sassafras, Lobelia, Senna, Mandrake, Yohimbine	Artemisia absinthium (wormwood plant), Periwinkle, Autumn crocus, Sassafras, Chuihong tuokuwan (Black Pearl), Tung shueh, Horse chestnut, Vandelia cordifolia	Alfalfa, Buckthorn, Ginger, Nettle, Vervain, Aloe, Capsicum, Ginseng, Noni juice, Bayberry, Cascara, Horsetail, Panax, Blue Cohosh, Coltsfoot, Licorice, Rhubarb, Broom, Dandelion, Mate, Senna

*Use of Herbal Supplements in Chronic Kidney Disease (CKD)*²⁰. It mentions that “*use of herbal supplements may be unsafe for CKD patients, since they are not able to clear waste products like a healthy person*”. Table 1 enlists the various herbs which have been implicated in renal injury.²⁰

The guidelines of the NKF make it amply clear that even a healthy person should exercise a lot of caution before venturing to take herbal drugs. It mentions that “natural does not always mean safe”

This article is not in any way against herbal medicines but in this era of evidence-based medicine, it is pertinent for each of us to base our decisions on the available evidence. Although, the principles of Ayurveda were enunciated long time back and it were based on good scientific evidence, but as of today a lot of research needs to be put and integration with the modern system of medicines is required to pave the way for evidence-based herbal medicine which could benefit all and sundry.

There is some evidence about herbs which are **nephroprotective** or beneficial to the kidneys⁵, and this article shall conclude with a word about them. Silymarin derived from milk thistle (*Silybum marianum*) seeds contains several potent antioxidant flavonolignans. Silymarin has renal protective effects in animals due to its antioxidant effects against damaging free radicals and by virtue of stimulating RNA and protein synthesis which is important for renal & hepatic repair mechanisms. Silymarin also protects kidney cells in culture from drug-induced nephrotoxicity²¹ and also protects against experimental cyclosporine nephrotoxicity.²² Picroliv (*Picrorhiza kurroa*), a popular medicinal Ayurvedic herb and its extracts from the roots

and rhizomes protected the kidney in a renal ischemia-reperfusion induced injury model in rats²³. Astragalus (*Astragalus membranaceus*), a popular Chinese herb, is effective against experimentally induced glomerulonephritis in rats, especially in reducing proteinuria. Cordyceps (*Cordyceps sinensis*), a fungus found growing in caterpillar larvae of certain moths, is valued as a kidney tonic in China. The Japanese traditional remedy Saireito, a 12 herb mixture, has also been found to be renoprotective. Extracts from the root of *Salvia miltiorrhiza* (Danshen) along with fructose 1-6 diphosphate prevented the decline of renal cortical Na-K-ATPase activity induced by ischemia and gentamicin in rats. Extracts of the plant *Herniaria hirsute* inhibit calcium oxalate crystal aggregation and thus may be useful in preventing kidney stone formation. However, similar benefits when demonstrated in human studies will define the place of herbal drugs in nephroprotection.

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