

Nephrotoxic Potential of Herbal Drugs.

Narinder P Singh, Anupam Prakash*

Department of Medicine, Maulana Azad Medical College &

*Lady Hardinge Medical College, New Delhi, India

The Government of India has supported and opened ventures in the field of complementary and alternative medicine (CAM) during the last one decade this 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. 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. 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 herbal supplements. Moreover, over two-thirds of people using alternative therapies did not report this piece of information to their health care providers¹. 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. 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 harbouring 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. Several factors have been identified which make the kidney vulnerable to toxic injury due to indigenous medicines. These include urine pH, high blood flow rate, high endothelial surface area, high metabolic activity, active uptake by tubular cells and medullary interstitial concentration. The toxins may injure the tubules directly, at the site of toxin transport or concentration, or by inducing renal ischemia, hemoglobinuria or myoglobinuria². 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 are the most frequently encountered. Various

herbal agents that are known to be toxic can be classified into (i) agents which are directly nephrotoxic, (ii) herbal drugs which result in electrolyte abnormalities by acting upon the kidney, (iii) agents which can predispose to formation of stones (oxalate stones), (iv) agents which act as diuretics, (v) herbal drugs which contain heavy metals or other drugs and (vi) herbal agents which can interact with other drugs specially in the renal transplanted subject³.

HERBS WHICH ARE DIRECTLY NEPHROTOXIC

1. Chinese herb nephropathy or Aristolochic acid nephropathy⁴⁻⁸

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 usage⁸. 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 suggested⁹. 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

This condition has been reported from the Balkan states, resulting from plant products contaminated by the fungal mycotoxin ochratoxin A, which also forms mutagenic DNA products in kidney tissue. However, the exact aetiology of Balkan endemic nephropathy is still a mystery¹⁰.

3. Djenkol bean poisoning (Djenkolism)¹¹⁻¹³

This 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, haematuria, 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 with in 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 sulphur 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 Africa¹⁴. Symptoms appear in 1-4 days in >70% cases manifesting as nausea and vomitings followed by hypoglycaemia 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 failure¹⁵. 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 juices¹⁶.

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 nephropathy¹⁷.

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)* these 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 apiole. 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 arsenic. 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.

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- *Use of Herbal Supplements in Chronic Kidney Disease (CKD)*¹⁸. 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. Some facts have been enlisted about herbs that every CKD patient should know:*

- *Very few herbs have been studied in CKD patients. What may be safe for healthy persons may not be safe for someone with CKD, and in fact, could be dangerous. Therefore, you need to be very cautious about your use of these products.*
- *The government does not regulate herbal supplements, so the exact content of these products is unknown.*
- *Without regulation, there are no requirements for testing, so the purity, safety and effectiveness of the products are unknown.*
- *Herbal preparations are subject to contamination (may contain*

toxic heavy metals such as lead or mercury).

- Products may contain minerals harmful to CKD patients, for example: potassium.

Some herbs that may serve as diuretics may also cause “kidney irritation” or damage. These include bucha leaves and juniper berries. Uva Ursi and parsley capsules may have negative side effects as well.

Many herbs can interact with prescription drugs. A few examples are St. Johns Wort, echinacea, ginkgo, garlic, ginseng, ginger, and blue cohosh. Transplant patients are especially at risk, as any interaction between herbs and medications could potentially put them at risk for rejection or losing the kidney. It is important to ask your doctor and/or pharmacist about any herbs or medicines you want to take to avoid potential problems.

Herbs that may be toxic to the kidneys

Artemisia absinthium (wormwood plant)	Periwinkle
Autumn crocus	Sassafras
Chufong tuokuwan (Black Pearl)	Tung shueh
Horse chestnut	Vandelia cordifolia

Herbs that may be harmful in chronic kidney disease

Alfalfa	Buckthorn	Ginger	Nettle	Vervain
Aloe	Capsicum	Ginseng	Noni juice	
Bayberry	Cascara	Horsetail	Panax	
Blue Cohosh	Coltsfoot	Licorice	Rhubarb	
Broom	Dandelion	Mate	Senna	

Herbs known to be unsafe for all people

Chapparal	Pennyroyal
Comfrey	Pokeroot
Ephedra (Ma Huang)	Sassafras
Lobelia	Senna
Mandrake	Yohimbe

These lists are not necessarily complete. More information regarding the use of herbs will become available over time. You are encouraged to proceed with caution with all herbal preparations and use them only under the direction of your medical team.

With all of these cautions, perhaps you are wondering if use of any herbs is a good idea. The use of common herbs, in normal amounts, when cooking is just fine and typically recommended to enhance the flavor of foods on a low-sodium diet.

So, before you take any herbal supplement, it is recommended:

- Checking with your doctor, dietitian, pharmacist and/or product manufacturer regarding safety, dosage, duration of use, interactions with prescription drugs, etc.
- Use only standardized herbal extracts made by reputable companies.
- Never take more than the recommended dosage, or longer than recommended.
- Do not use herbal remedies for serious illness.
- Do not use herbs if considering pregnancy.

Remember ... natural does not mean safe, especially for CKD patients. Be smart and ask questions before using any herbal products.

Although the above guidelines of the NKF (italicised) are for CKD patients, it is amply clear from the text that even a healthy person should exercise a lot of caution before venturing to take herbal drugs.

Are some herbs Nephroprotective also?

There is some evidence about herbs which are nephroprotective or

beneficial to the kidneys³, 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 nephrotoxicity¹⁹ and also protects against experimental cyclosporine nephrotoxicity²⁰. Picroliv (*Picrorhiza kurroo*), 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 rats²¹. 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 Sairei-to, a 12 herb mixture, has also been found to be renoprotective. Extracts from the root of *Salvia miltioriza* (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.

In conclusion, 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 is 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.

REFERENCES

1. Onopa J. Complementary and alternative medicine (CAM): a review for the primary care physician. *Hawaii Med J* 1999; 58(2): 9-19.
2. Nand N, Aggarwal HK, Jai D, Sharma M. Indigenous drug induced nephropathy. In: Sahay BK (ed). *Medicine Update 2006*; vol. 16, 458-462.
3. Combet W, Newton M, Combet A, Kosier JH. Effects of herbal supplements on the kidney. *Urologic Nursing* 2005; 25(5): 381-386, 403.
4. Lord GM, Tagore R, Cook T, Gower P, Pusey CD. Nephropathy caused by Chinese herbs in the UK. *Lancet* 1999; 354 (9177): 481-482.
5. Lord GM, Cook T, Arlt VM, Schmeiser HH, Williams G, Pusey CD. Urothelial malignant disease and Chinese herb nephropathy. *Lancet* 2001; 358 (9292): 1515-1516.
6. Nortier JL, Martinez MC, Schmeiser HH, et al. Urothelial carcinoma associated with the use of a Chinese herb (*Aristolochia fangchi*). *NEJM* 2000; 342 (23): 1686-1692.
7. Cosyns JP, Jadoul M, Squifflet JP, Wese FX, van Ypersele de Strihou C. Urothelial lesions in Chinese-herb nephropathy. *AJKD* 1999; 33 (6): 1011-7.
8. Vanherweghem JL, Depierreux M, Tielemans C, et al. Rapidly progressive interstitial renal fibrosis in young women: association with slimming regimen including Chinese herbs. *Lancet* 1993; 341(8842): 387-91.
9. Vanherweghem JL, Abramowicz D, Tielemans C. Effects of steroids on the progression of renal failure in chronic interstitial renal fibrosis: a pilot study in Chinese herb nephropathy. *AJKD* 1996; 27: 209-215.
10. Tatu CA, Orem WH, Finkelman RB, Feder GL. The etiology of Balkan endemic nephropathy: still more questions than answers. *Environ Health Perspect* 1998; 106(11): 689-700.
11. Segasothy M, Swaminathan M, Kong NC, Bennett WM. Djenkol bean poisoning (djenkolism): an unusual cause of acute renal failure. *AJKD* 1995; 25(1): 63-66.
12. Wong JS, Ong TA, Chua HH, Tan C. Acute anuric renal failure following jering bean ingestion. *Asian J Surg* 2007; 30(1):80-81.
13. H'ng PK, Nayar SK, Lau WM, Segasothy M. Acute renal failure following jering ingestion. *Singapore Med J* 1991; 32(2): 148-149.
14. Seedat VK. Acute renal failure among blacks and Indians in South Africa. *S Afr Med J* 1978; 54: 27-431.
15. Bednarova V, Bodlakova B, Pelclova D. Mushroom poisoning by *Cortinarius orellanus*. *Cas Lek Cesk* 1999; 138(4): 119-121.
16. Mueller BA, Scott MK, Sowinski KM, Prag KA. Noni juice (*Morinda citrifolia*): hidden potential for hyperkalemia? *AJKD* 2000; 35(2): 310-312.
17. Chen CL, Fang HC, Chou KJ, Wang JS, Chung HM. Acute oxalate nephropathy after ingestion of star fruit. *AJKD* 2001; 37(2):418-422.
18. <http://www.kidney.org/ATOZ/atocitem.cfm?id=123> National Kidney Foundation website -Kidney Disease- A to Z health guide- Use of herbal supplements in Chronic Kidney Disease.
19. Sonnenbichler J, Scalera F, Sonnenbichler I, Weyhenmeyer R. Stimulatory effects of silybinin and silychristin from the milk thistle *Silybum marianum* on kidney cells. *J Pharmacol Exp Ther* 1999; 290(3): 1375-1383.
20. Zima T, Kamenikova L, Janebova M, Buchar E, Crkvska J, Tesar V. The effect of silybinin on experimental cyclosporine nephrotoxicity. *Ren Fail* 1998; 20(3): 471-479.
21. Seth P, Kumari R, Madhavan S, et al. Prevention of renal ischemia-reperfusion-induced injury in rats by picroliv. *Biochem Pharmacol* 2000; 59(10): 1315-1322.