Effects of Herbal Supplements On the Kidney

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A recent and frequently cited survey of alternative medicine revealed that 42% of Americans use alternative therapies, with 12% of these therapies being the use of herbal supplements at a cost of $5 billion annually. Furthermore, 60% of people using alternative therapy do not report this information to their health care providers (Eisenberg, Davis, & Ettner, 1999). One problem with dietary supplement use is lack of consistent requirements for rigorous safety, efficacy, and purity testing resulting in varying amounts of active constituents from batch to batch.

Although herbal medicine use continues to grow in many disease conditions, the risk from use may over shadow potential benefit, especially in the renal compromised patient population (Foote & Cohen, 1998; Isnard et al., 2004). Vulnerable times for the renally compromised patient include predialysis, dialysis, and the post-renal transplant periods. They may also be confronting co-morbid disease states such as hypertension or diabetes. Renal patients may reach for additional therapy in the form of herbal dietary supplements because they experience adverse side effects or lack of efficacy from conventional medicines.

Plants with Known Direct Renal Toxicity

The most dramatic and highest profile case of herbal nephrotoxicity occurred from 1990-1992 in over 100 people in Belgium who ingested a Chinese weight loss/slimming remedy containing aristolochic acid principally from the plant *Aristolochia fangchi* (Vanherweghem et al., 1993). Seventy of these patients required renal transplants or dialysis and 30 subsequently developed urothelial carcinoma. In 2000, the FDA identified two new cases of interstitial renal fibrosis from aristocholic-containing herbal products. The resulting nephropathy is referred to as "aristolochic acid nephropathy" or less accurately "Chinese herb nephropathy." Aristolochic acid is a nitrophenanthrene carboxylic acid which forms DNA adducts in renal as well as other tissues after metabolic activation (Volker, Stiborova, & Schmeister, 2002). 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. Aristolochic acid is found in several other plants particularly in the *Asarum* and *Bragantia* genera. Hundreds of additional cases have been reported in several European and Asian countries since these early reports in Belgium. The FDA has imposed strict guidelines to prevent any Chinese herbal products containing aristolochic acid from entering the U.S. market.

A similar type of nephropathy has been reported in the Balkans and has been termed "Balkan endemic nephropathy" (Tatu, Oren, Finkelman, & Feder, 1998). The causative agent in this type of nephropathy is plant products contaminated by the fungal mycotoxin ochratoxin A. It also forms mutagenic DNA adducts in renal tissue which likely underlies the observed pathology.

Many traditional medicines and foods especially in the tropical regions of Africa and Asia contain renal toxic plants. One such food/medicine is the djenkol bean, a pungent smelling edible fruit of the hardwood tree *Pithecellobium labatum* (Areekul, Kirdudom, & Chaovanapricha, 1976). A 70% ethanol extract of the djenkol bean containing the toxic compound djenkolic acid was fed to monkeys, rats, and mice. Histologic examination of their kidneys showed severe tubular necrosis with a lesser degree of glomerular cell necrosis. A traditional remedy in South Africa called "Impila" is made from the roots of the plant *Callilepis laureola*. It is used to treat a number of conditions and has marked hepatic and renal toxicity. The renal damage caused

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is characterized by acute proximal convoluted tubule and loop of Henle necrosis which can lead to kidney failure (Stewart, Steenkamp, van der Merwe, Zuckerman, & Crowther, 2002).

There have been reports of acute renal failure in individuals ingesting wild mushrooms containing the nephrotoxin orellanine (Mount, Harris, Sinclair, Finlay, & Becker, 2002). Renal biopsy showed marked tubular interstitial nephritis and fibrosis. There has been one case report of acute renal failure in a patient with systemic lupus erythematosus taking the popular Peruvian herb cat's claw (*Uncaria tomentosa*) (Hileps, Bellucci, & Mossey, 1997).

Herbs That May Alter Serum Potassium Or Contain Oxalic Acid

Several medicinal plants have the potential to alter plasma levels of potassium resulting in either hypokalemia or hyperkalemia. Licorice root (*Glycyrrhiza glabra*), especially when used at high doses and for prolonged periods, has a well-known pseudoaldosterone-like effect on the reabsorption of sodium and potassium (Stewart et al.,1987). Sodium retention is increased, potentially increasing blood pressure with a corresponding decrease in K^+ leading to hypokalemia. Hypokalemia may in turn increase the toxicity of drugs such as digoxin by increasing its binding to cardiac membranes. The mechanism of this effect relates to glycyrrhizic acid in licorice root being hydrolyzed to glycyrrhetenic acid which is an inhibitor of renal 11-hydroxysteroid dehydrogenase. This enzyme catalyzes the inactivation of cortisol to cortisone. Cortisol accumulates in the kidney and stimulates the aldosterone receptors in cells of the cortical collecting duct thus increasing Na^+ reabsorption (Funder, Pearce, Smith, & Smith, 1988).

Several herbal remedies taken as laxatives contain active compounds called anthraquinones. The laxative herbs senna (*Senna alexandria*), cascara sagrada (*Rhamnus purshiana*), and rhubarb (*Rheum officinale*) can lead to electrolyte imbalance especially hypokalemia (Westendorf, 1993). Another herbal supplement of possible concern to the renal patient is noni juice. Juice made from the noni fruit (*Morinda citrifolia*) could contribute to the development of hyperkalemia due to its high content of potassium (56.3 mEq/L) (Mueller, Scott, Sowinski, & Prag, 2000). Dandelion (*Taraxacum officinale*), stinging nettle (*Urtica dioica*), horsetail (*Equisetum arvense*), and alfalfa (*Medicago sativa*) are also high in potassium (Leung & Foster, 1996). Plants high in oxalic acid such as rhubarb (*Rheum officinale*) may increase the formation of kidney stones (Leung & Foster, 1996). There has also been a report of acute oxalate nephropathy following ingestion of star fruit (*Averrhoa carambola*) (Chen, Fang, Chou, Wang, & Chung, 2001).

Medicinal Plants with Diuretic Activity

These herbs may be of particular interest to patients pre-dialysis who believe that they may be able to stimulate their declining kidney function and thus delay the need for dialysis. The following herbs have traditional use as diuretics: 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*) (Fetrow & Avila, 1999). These herbs with varying degrees of diuretic activity require caution even in healthy individuals but should be especially a concern for the renal-compromised patient. Most of these herbs should more accurately be called "aquaretics" in that they increase glomerular filtration rate and urine output but do not stimulate electrolyte secretion. Some act as direct tubular cell irritants and others may alter serum electrolytes with resultant cardiovascular consequences.

Juniper berries contain terpine-4-ol in the volatile oil fraction which may cause kidney irritation and damage in excess (Newall, Anderson, & Phillipson, 1996). 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 (Newall et al., 1996). Also in Germany, dandelion, horsetail, and uva ursi are licensed as standard medicinal teas to stimulate diuresis.

Herbal Products Adulterated with Drugs And Heavy Metals

There have been many reports especially of Chinese and Ayurvedic herbal products containing nephrotoxic heavy metals such as lead, mercury, cadmium, and arsenic (Espinosa, Mann, & Bleasdell, 1995; Keen, Deacon, Delves, Moreton, & Frost, 1994; Wu, Hong, Lin, Yang, & Chien, 1996). To add to the complication, many heavy metals are considered medicinal in these medical systems but their presence in some imported formulations are not revealed on their labels. In addition some of these same herbal products contain pharmaceutical drugs. Formulations containing nonsteroidal anti-inflammatory drugs (NSAIDs) may lead to renal failure via changes in intrarenal blood flow. Another example is a case where a Chinese herbal formula contained the drug phenylbutazone which caused analgesic nephropathy (Segasothy & Samad, 1991). The California Department of Health Services recently screened 260 imported Asian patent medicines and found that 83 contained undeclared drugs or heavy metals (Marcus & Grollman, 2002).

Herbs and the Transplant Patient

The transplant patient is also at risk for complications from herbal remedies such as Echinacea (*Echinacea purpurea*), which is promoted as an immune system stimulant (Combest & Nemecz, 1997). This effect could endanger the transplant

Table 1.
Nephro-Toxic Herbs and Dietary Supplements

Herbs or Plants	Renal Effect	Comments
Aristolochia fangchi	Interstitial renal fibrosis, urothelial carcinoma	• FDA prohibits U.S. entry of products containing aristocholic acid. • Found in some supplements for reducing weight
Djenkol bean (*Pithecellobium labatum*)	Tubular and glomerular cell necrosis	Pungent-smelling tropical fruit from Africa and Asia
Impila (*Callilepis laureola*)	Necrosis of proximal tubule and loop of Henle	Also hepatotoxic
Wild mushrooms	Tubular interstitial nephritis and fibrosis	Prellanine is the known toxin
Cat's claw (*Uncaria tomentosa*)	Acute renal failure	One report (Hileps et al., 1997)
Licorice (*Glycyrrhiza glabra*)	Hypernatremia, hypokalemia	Chronic high dosages increase blood pressure and digitalis/digoxin toxicity
Senna (*Senna Alexandria*), cascara sagrada (*Rhamnus purshiana*); rhubarb (*Rheum officinale*)	Hypokalemia	Most likely in cases of chronic laxative use
Noni fruit (*Morinda citrifolia*)	Hyperkalemia	Juice contains high potassium concentration
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*); alfalfa (*Medicago sativa*).	Increase diuresis of water without electrolytes	Can cause clinically dangerous imbalances of serum electrolytes
Some Asian, Chinese, and Ayurvedic herbal products may contain heavy metals (lead, mercury, cadmium, and arsenic) and unlisted drugs (nonsteroidal anti-inflammatory drugs [NSAIDs])	Nephrotoxicity	Persons with renal and cardiovascular disease should avoid all such products
Echinacea (*Echinacea purpurea*)	Increased probability of transplant rejection	Counteracts action of immunosuppressant drugs, such as cyclosporine
St. John's wort (*Hypericum perforatum*)	Increased probability of transplant rejection	Increases hepatic metabolism of cyclosporine

patient taking immunosuppressant drugs. Furthermore, St. John's wort (*Hypericum perforatum*) causes a decrease in cyclosporine, an immunosuppressant, serum levels thus compromising the success of the organ transplant (Mandelbaum, Pertzborn, Martin-Facklam, & Wiesel, 2000). Although not yet demonstrated, many other herbal supplements may have a similar effect on the metabolism of cyclosporine as well as other drugs used to treat the transplant patient (see Table 1).

Nephro-Protective Herbs and Dietary Supplements

Milk thistle (*Silybum marianum*) seeds contain-

Table 2.
Nephro-Protective Herbs and Dietary Supplements

Herb or Supplement	Protective Effect	Comments
Milk thistle (*Silybum marianum*) seeds	Antioxidant flavonolignans demonstrated renal protective effects in rodent from toxins to include drugs like cisplatin.	Hepatoprotective also; need more human studies.
Picroliv (*Picrorhiza kurrooa*)	Extracts from roots and rhizomes demonstrated protection against various renal toxins.	Hepatoprotective also; need more human studies.
Astragalus (*Astragalus membranaceus*)	Studies demonstrated effect against experimentally induced glomerulonephritis in rats and in patients with chronic glomerulonephritis by reducing proteinuria.	Popular herb used in Chinese traditional medicine.
Cordyceps (*Cordyceps sinensis*)	Anti-oxidant protective mechanism improved renal function as measured by creatinine clearance; lessened the nephrotoxicity of cyclosporine in kidney transplant patients.	Fungus found growing in caterpillar larvae of certain moths valued as a kidney tonic in China.
Sairei-to, 12 herb mixture	Kidney protection in gentamicin induced renal toxicity, IgA nephropathy, and lupus nephritis in human and animal studies.	Japanese traditional remedy.
Salvia miltiorriza root extracts	Along with fructose 1-6 diphosphate prevented the decline in renal cortical Na-K-ATPase activity induced by ischemia and gentamicin.	Traditional Chinese remedy called Danshen.
Herniaria hirsute aqueous extracts	Inhibits calcium oxalate crystal aggregation.	May be beneficial in preventing kidney stones.

Source: Fetrow & Avila, 1999

ing several potent antioxidant flavonolignans collectively called silymarin have both hepatic and renal protective effects in rodent models (Combest, 1998). The main constituents composing silymarin are silibinin, silicristin, isosilibinin, and silidianin. Silibinin and silicristin, aside from their antioxidant effects against damaging free radicals, also stimulate RNA and protein synthesis which is important for renal and hepatic repair mechanisms. In addition these same flavonolignans protect kidney cells in culture from the renal toxic effects of the drugs paracetamol, cisplatin, and vincristine (Sonnenbichler, Scalera, Sonnenbichler, & Weyhenmeyer, 1999). Another study in rats demonstrated that silibinin protected renal tubular cells from the oxidative damage from cisplatin (Gaedeke, Fels Bokemeyer, Mengs, Stolte, & Lentzen, 1996). Silibinin also protects against experimental cyclosporine nephrotoxicity (Zima et al., 1998).

Another potentially useful nephro-protective medicinal herb popular in Ayurvedic medicine is picroliv (*Picrorhiza kurrooa*). Extracts from the roots and rhizomes offer protection against various hepatic and renal toxins. Picroliv protects the kidney in a renal ischemia-reperfusion induced injury (IRI) model in rats (Seth et al., 2000). Pretreatment of rats orally with picroliv for 7 days before initiation of experimental IRI lowered renal lipid peroxidation, reduced apoptosis, and generally increased the viability of renal cells. Another study in rats found that oral administration of picroliv to rats exposed to the carcinogen 1,2 dimethylhydrazine decreased the extent of renal necrosis (Rajeshkumar & Kutton, 2003). As with milk thistle animal studies using picroliv support their potential clinical benefit as nephro-protectants. However, human clinical studies are needed to confirm these results in cell culture and animal models.

Astragalus (*Astragalus membranaceus*), a popular herb used in Chinese traditional medicine, is effective against experimentally induced glomerulonephritis in rats, especially in reducing protein-

uria (Su et al., 2000). Several clinical studies also showed a reduction in proteinuria in patients with chronic glomerulonephritis by Astragalus (Shi et al., 2002). Cordyceps (*Cordyceps sinensis*), a fungus found growing in caterpillar larvae of certain moths, has long been valued as a kidney tonic in China (Zhu, Halpern, & Jones, 1998). One study in 61 patients with lupus nephritis showed that a combination of 2 g to 4 g of cordyceps powder together with 0.6 grams of artemisinin from the plant *Artemisia annua* for 3 years improved kidney function as measured by creatinine clearance (Lu, 2002). Another study found that cordyceps lessened the nephrotoxicity of cyclosporine in kidney transplant patients (Xu, Huang, Jiang, Xu, & Mi, 1995). An antioxidant protective mechanism was postulated for this protective effect. The Japanese traditional remedy Sairei-to, a 12 herb mixture, has shown in human and animal studies to protect the kidney in gentamicin renal toxicity, IgA nephropathy, and lupus nephritis (Ohno et al., 1993). Another study in rats showed that extracts from the root of the plant *Salvia miltiorriza* (Danshen) along with fructose 1-6 diphosphate prevented the decline of renal cortical Na-K-ATPase activity induced by ischemia and gentamicin (Lu & Li, 1989). Further, extracts of the plant *Herniaria hirsute* inhibit calcium oxalate crystal aggregation and thus could be useful in preventing kidney stone formation (Atmani & Khan, 2000). In summary, there seems to be many potentially protective medicinal plants and supplements that may protect the kidney perhaps via acting primarily as anti-oxidants (see Table 2).

Nursing Care

The nurse may be one of the first members of the health care team to be approached by the patient using or contemplating the use of an herbal product for renal failure symptoms. The nurse should establish dialogue with patients regarding use of herbal supplements which affect the kidney. The nurse should be armed with information and legitimate Internet sources regarding the effect of dietary supplements on the kidney. As nurses, we want to be proactive during the routine history and physical and include questions such as "Tell me about any herbal supplements you may be using because we want to provide the safest care possible for you and need to know all medications and supplements you take. Some prescribed medications may interact with the supplements and some may affect kidney function." The nurse should also have evidence-based herbal dietary supplement references to share with patients such as the *Professional's Handbook of Complementary and Alternative Medicines* published by Amazon Books and the Natural Medicines Comprehensive Database available online and in print (Barrett, 2000). Table 3 lists interventions to facilitate safe care for renal patients using herbal dietary supplements.

Table 3.
Approaches to Facilitate Safe Care for Renal Patients Using Herbal Dietary Supplements

1. Obtain a thorough history of renal symptoms and measures used for relief of them.
2. Obtain a thorough medication history to include:
   - prescription medications
   - herbals and other complementary (alternative) therapies
   - over-the-counter medications (OTCs)
   - caffeine, alcohol, and nicotine
   - illicit agents
3. Ask if patient has any allergies, is pregnant or breast-feeding.
4. Encourage patient to discuss herbals and other complementary therapies, remember the majority of patients will not mention herbal use.
5. Accept that patients may use complementary therapies and maintain a positive attitude. They fear criticism from their medical caregivers. Ask open-ended questions such as "Some patients forget or fear mentioning herbal use with the health care team, I wonder about you?"
6. Reinforce that you are asking questions to avoid potential drug interactions between prescribed medications and complementary therapies as the best standard of care.
7. Obtain continuing education to learn about complementary therapies and sources of information to share with patients.
8. Document your discussion with patient regarding use of herbals.
9. Counsel against herbal use if pregnancy is questionable, during known pregnancy or lactation.
10. Lack of FDA standards may result in reduced herbal content and efficacy. Teach patient to read labels in terms of word "standardized" on label as well as amounts and percents of ingredients.
11. Find out reason patient is using herbals.
12. Infants, children, elderly should not use herbals without consultation with health care provider.
13. Caution patients to use herbs in recommended doses and inform prescriber and other caregivers of undesired side effects.
14. Teach patient to pay attention to kidney and other body symptoms and obtain medical help rather than use complementary options without medical evaluation of condition.
15. Encourage patient to purchase herbals and other supplements from a reputable pharmacy.
16. Encourage patient referral expert in herbals and complementary medicine if they seek this option.
17. Teach patient not to share herbals with others.
18. Teach patient to keep herbals out of reach of children and pets.
19. Caution patient that herbals may not substitute for proven traditional medicine; encourage patient to explore his/her use of herbals in overall health care practice with prescriber or others involved in care.

Source: Cingliano & Sun, 1998

Conclusion

The increased patient use of alternative medicine requires the nurse to be aware of potential risks and benefits that alternative medicines may offer. Nephrotoxic plants containing aristolochic acid and djenkol bean must be avoided in all patients but especially in renal-compromised patients. Other herbal remedies such as licorice root, senna, cascara, and rhubarb may alter serum potassium values or increase the risk of kidney stones high in oxalic acid. Transplant patients must be made aware of the potential risk of complications from Echinacea and St. John's wort as these medicinal plants may cause a decrease in the effect of immunosuppressant drugs. In summary, the nurse plays a vital role in monitoring the ingestion and effects of herbal supplements in the renal-compromised patient. ⊡

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