Natural Medicines Causing Acute Kidney Injury

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Summary: The use of alternative remedies derived from plants and animals is increasing worldwide. Their source and composition varies depending on the prevalent local practices. They are not tested for efficacy and safety; their ingredients are unknown and the dosage and route of administration are not standardized. Potentially toxic chemicals are added to them to increase their potency and mistaken identity has led to the use of toxic plants instead of the originally intended herb. Kidneys play a vital role in the metabolism and excretion of these substances and acute kidney injury is a common and important manifestation of their toxicity. The most usual renal lesions include acute tubular necrosis, cortical necrosis, and interstitial nephritis. Patients often present late to hospitals with multi-organ involvement. The diagnosis may be missed if the history is not sought specifically. These factors culminate in high mortality rates. Study of this entity is difficult because of the remoteness of the areas, unfamiliarity with local cultures, and mystery and secrecy surrounding the natural medicines used. Physicians need to be aware of this condition to make a timely diagnosis and provide appropriate management. Public awareness and regulation of the use of these medicines are required to eradicate this entity from the community.

Semin Nephrol 28:416-428

Keywords: *Acute kidney injury, natural medicines, alternative medicines, developing countries, health care costs*

For centuries, mankind has looked towards natural sources to find remedies for illnesses. References to natural medicines in which plants were used as therapeutic substances can be found in ancient literature. Even in modern times, they continue to form the backbone of our pharmacies; more than 50% of drugs used in Western pharmacopoeia are either isolated from herbs or are derived from modification of chemicals first found in plants or other natural sources.[1,2] Some of the earliest examples of drugs derived from botanical sources that continue to be used widely even today include digitalis and quinine.

Throughout the developed world, therapeutic substances in common use are now produced under good manufacturing practice (GMP) conditions in modern plants of pharmaceutical companies. Still, about 65% to 80% of the population in underdeveloped countries continue to use natural medicines in their crude form for treatment of their illnesses.[3] In Africa, up to 80% of the population depends on traditional medicine for primary health care whereas in China, herbal preparations account for up to 50% of the total consumption of pharmaceutical agents. In economic terms, the global annual turnover in herbal medicines is estimated to be $60 billion, representing about 20% of the overall drug market.[4] In India, 60% of the population lives in rural areas and depend on local practitioners or traditional healers for their health problems, most of whom prescribe herbs.[5]

The use of herbal medicine has increased substantially in developed countries in recent years.[6] In the United States, a survey conducted in 1997 determined that 12.1% of adults had used an herbal medicine in the previous 12 months, resulting in out-of-pocket payments of $5.1 billion.[7] This figure represented a 400%

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0270-9295/08/$ - see front matter
 doi:10.1016/j.semnephrol.2008.04.010

increase compared with that 1990. In 2001, Americans spent US $17.8 billion on dietary supplements, and $4.2 billion for herbs and other botanical remedies.[8] A survey of more than 3,000 Australians found that herbal medicine accounted for approximately 26% of all alternative and complementary medicine use.[9]

HERBAL MEDICINE TOXICITY

There are many reasons for the popularity of natural medicines. In the economically poor countries, a combination of ignorance, poverty, nonavailability of health facilities, high cost of modern medicines, and the widespread belief in indigenous systems forces the people to turn to local exorcists, faith healers, and witch doctors for their medical needs.[10-12] Many cultures, especially those on the African continent, believe that a disease state reflects disharmony between the person and their ancestors. The traditional healer consults the spirits to find this disharmony and to appease the ancestors to cure the problem. In some countries, traditional systems of medicine have been supported by the World Health Organization, incorporated into the local health system, and given equal status with Western medicine by the local governments.[5]

Even in the developed world, the search for perfect but as yet elusive holistic medicine has been given new momentum by several groups such as New Age, postmodernist, and ecoradicalist movements, and their followers increasingly are turning to alternative sources. Patients suffering from chronic diseases feel disenchanted with Western medicine because of the cost, complexity, and perceived limitations. The highly publicized recalls of some prescription drugs have contributed to a loss of trust in the safety of Western medicine. These remedies offer the convenience of easy availability and low cost. Other reasons for their widespread use include the belief that traditional medicines are good and innocuous,[13] and a strong placebo effect from the rituals associated with the ingestion of herbal medicines.[14] The belief that these remedies are gentler and therefore harmless is widespread. Herbal remedies often are classified for regulatory and marketing purposes as dietary supplements and hence are exempt from rigorous safety testing. According to the US Dietary Supplement and Health Education Act, the onus of establishing the safety of herbal medicines is not on the Food and Drug Administration, which frees the dietary supplement industry from Food and Drug Administration oversight. It has been suggested that dietary supplements are subject to lower safety standards than even food additives.[7]

In recent years, the medical community increasingly has recognized the potential of natural medicines to cause harm to various organ systems, including the kidneys.[5] The most important clue for establishing a cause-and-effect relationship is shown by the clear temporal association between the intake of these agents and the injury. This is easier in the case of acute kidney injury (AKI), in which the presentation is relatively dramatic and the history of the use of the offending agent is easier to recall. In contrast, a history of past exposure is relatively harder to elicit in chronic kidney disease and more sophisticated laboratory techniques are required to prove causality.

Systematic study of patients using traditional remedies is not straightforward. In many societies, patients resort to Western medicine only after folk treatments fail or a complication ensues. Even after patients present to hospitals, there is much secrecy surrounding the use of folk remedies because of the fear of stigmatization or social pressures. The history of natural medicine use is not sought by uninformed physicians or is denied by the patient, even to friends and family, especially when the query is in threatening or punitive tones. Witch doctors are supposed to possess magical powers because of their knowledge of witchcraft and sorcery, and hence are feared by the community. Fear of a curse or retribution is responsible for patients' denial. These facts make it almost impossible to obtain accurate statistics as to the frequency of the use of folk remedies in the hospitalized population and to determine their true impact on morbidity and mortality.

AKI DUE TO HERBAL MEDICINES

AKI may be the sole manifestation or develop as part of a multisystem involvement that may include acid-base disturbances, liver failure,

neurologic abnormalities, disseminated intravascular coagulation, or respiratory failure. The importance of toxic AKI caused by indigenous medications has been highlighted in reports emerging from sub-Saharan Africa and parts of Asia.[5] According to some experts, poisoning with traditional medicines is one of the main causes of high mortality rates in many African countries. In Ga-Rankuwa Hospital in Pretoria, traditional medicines were responsible for 18% of all acute poisonings and more than 85% of all deaths from acute poisoning. The main source was the traditional healer.[15] At least 8 remedies were associated with hematuria and renal failure. About a quarter of all cases of acute renal failure (ARF) as a result of medical causes seen over a 2-year period at the University of Nairobi in Kenya were related to the use of herbal remedies.[16] In another series from Africa, a third of 150 cases of ARF were caused by an herbal medication.[17] Similar figures have been reported from several other African hospitals.[18,19] Among the toxic causal agents, herbs were involved in 50% of cases and the AKI was severe enough to require dialysis in about 60% of cases.[20] In fact, natural medicines are one of the most important causes of AKI in many African hospitals.

In a recent retrospective analysis of 78 patients (50 males, 28 females) with folk remedy–induced AKI, Luyckx et al[21] were unable to find an etiologic agent in the majority of cases. The remedies were consumed by mouth in 47%, as an enema in 10%, and through both routes in 13% of patients. Sixty-five percent of patients had severe renal failure, whereas 41% of patients had associated liver dysfunction. An important observation was the documentation of concomitant medical conditions in about 32% of patients, casting doubt on the etiologic relationship between the folk remedy and renal injury. The majority of patients presented with gastrointestinal symptoms, 68% of patients had dehydration or shock, which could have contributed to AKI.[21]

Because of a lack of access to health care, prognosis is heavily dependent on the timing of presentation, extent of involvement of other organs, and availability of dialytic therapy. The reported mortality rates vary from 24% to 75%. In the Luyckx et al[21] study, the overall mortality rate was 41%, and was comparatively higher in those requiring dialysis, in adults as compared with infants, in patients with liver dysfunction, and in human immunodeficiency virus–positive patients.

Sporadic descriptions of AKI caused by the use of natural medicines have appeared from the Western world, especially among immigrants from those parts of the world where such practice is common. One example of this was the report of ARF after ingestion of "holy water" in the United States by persons of Nigerian descent,[22] similar to the experience described from Nigerian hospitals.[20,23] This has been shown to be a form of hemoglobinuric ARF secondary to intravascular hemolysis caused by copper sulfate, with which this water is laced, giving it a green color and supposedly magical properties.

Little is known of the toxicology of most of the natural medicines, even when they have been identified. Plants used as medicines may be cultivated, but many are gathered from the wild by inexperienced people, which provide opportunities for mistakes and even deliberate substitution. Errors in plant identification can occur because of their confusing and overlapping terminology. Perhaps the most famous example of botanical mistaken identity involves Chinese herbal nephropathy in which the herb guang fang ji (*Aristolochia fangchi*) was substituted for han fang ji (*Stephania tetrandra*). The error remained undetected for 2 years, until patients started to develop renal failure in large numbers. Even after correct identification of a herb, lack of adherence to standard good manufacturing practice can lead to contamination with toxic compounds such as pesticides and even industrial chemicals.[5] Details of the composition of these medicines often are a closely guarded secret within families. Information is passed by word of mouth from generation to generation and great care is taken not to divulge the recipe to outsiders. Sources of toxins also include the freely available over-the-counter natural patent remedies that have been shown to be contaminated with substances including carbon tetrachloride, phenolphthalein, podo-

phyllum resin, aloe, potassium bromide, and potassium dichromate.[24,25]

Natural medicines often are administered in unusual ways. An important route of administration of these compounds is by enemas, especially in infants.[26] In one survey, about 63% of patients admitted to Baragwanath Hospital, serving a population of 2 million in Soweto, Johannesburg, admitted to be frequent enema users.[27] The enemas consisted of a mixture of herbs, barks, roots, leaves, and bulbs, and were administered through a truncated cow's horn or hollow reed. Members of the Zulu tribe receive up to 3 herbal enemas per week, and Swazi infants receive 50 enemas per year.[26,28] AKI has been reported after the use of these tribal enemas.[26]

In addition to medicines, natural substitutes used for other purposes also can cause AKI (eg, henna used as hair dye). Poisoning by a mixture of henna and paraphenylenediamine induces severe rhabdomyolysis, with angioneurotic edema involving the upper respiratory tract, often needing an emergency tracheostomy.[29] In Morocco, traditionally takaout el badia, a powder made of the seeds of *Tamaris orientalis*, is used by females for hair dye; however, in times of scarcity, it is replaced by takaout roumia, containing paraphenylenediamine.[30] Takaout is responsible for about 10% of all cases of ARF, 50% of all cases of rhabdomyolysis, 25% of ICU admissions for poisonings, and two thirds of poisoning-related deaths.[30]

Of the several histologic lesions that have been described after natural medicine–induced AKI, acute tubular necrosis, acute cortical necrosis, and acute interstitial nephritis are the most frequent.[5]

PATHOGENESIS OF NATURAL MEDICINE–INDUCED AKI

Kidneys are particularly vulnerable to toxic injury because of their high blood flow rate, large endothelial surface area, high metabolic activity, active uptake by tubular cells, medullary interstitial concentration, and low urine pH.[15] Renal tubules are involved in active transport and urinary concentration, and therefore the local concentration of these toxins is high, leading to direct injury to tubular cells. Other mechanisms include renal ischemia caused by volume loss or a hemodynamic effect on the vasculature, pigmenturia (hemoglobinuria or myoglobinuria), allergic interstitial nephritis, and systemic effects such as thrombotic microangiopathy or liver failure.

Adulteration of herbal medicines is common in many tropical countries. A government report found undeclared pharmaceuticals or heavy metals in 32% of Asian patent medicines sold in the state of California. These included ephedrine, chlorpheniramine, methyltestosterone and phenacetin, sildenafil, steroids, and fenfluramine; 10% to 15% had lead, mercury, or arsenic.[31] Out of more than 500 Chinese drugs, approximately 10% contained undeclared drugs or heavy metals[32,33]; ginseng dietary supplements sold in the United States contained the pesticides quintozene and hexachlorobenzene, or exceeded standards for lead content.[34] Sometimes drugs are added deliberately to herbs to enhance their efficacy. Abt et al[35] reported acute interstitial nephritis after consumption of a Chinese herb that had been contaminated with diazepam and mefenamic acid. The high heavy metal content of Chinese and Ayurvedic medicines may have originated from heavily polluted soil and irrigation water.[36] Dwivedi and Dey[37] found high lead and cadmium levels in the leaves of medicinal plants from India.

AKI also can result as a consequence of interactions of herbal medicines with conventional drugs. One example is the interaction between St. John's wort, derived from *Hypericum perforatum*, used for depression and anxiety, and drugs metabolized by enzymes of the hepatic cytochrome P450 family. St. John's wort induces cytochrome P450 activity[38] and thus can decrease plasma levels of drugs such as calcineurin inhibitors, which are substrates for the enzyme. In kidney transplant recipients, this interaction can precipitate AKI owing to allograft rejection.[39,40] Patients with kidney disease also are at increased risk of complications from herbal medicine, some examples are *Ginkgo biloba*–induced hemorrhagic complications, glyrrhizic acid–induced hypokalemia, and alfalfa or noni juice (*Morinda citrifolia*)–induced hyperkalemia.[41]

The following section describes some of the more important examples of AKI caused by natural remedies.

Callilepis laureola Poisoning

Callilepis laureola is a herb that grows widely in the countries of sub-Saharan Africa including South Africa, Zambia, Zaire, and Zimbabwe. The plant has a tuberous rootstock, and derives its name from the Zulu word *impila*, meaning health. An extract of the tubers is taken orally, as an enema, or as a douche.[42] Indications for its use include the following: for women for the prevention of bad dreams at the time of menarche, to induce fertility, and during pregnancy to ensure an easy childbirth; as a vermicide, decongestant, and for sexually transmitted diseases; for blood purification in the elderly and to ward off evil spirits. According to one estimate, impila is used by more than 50% of the population in Natal, and poisoning is among the most common cause of ARF in the black population of South Africa.[43,44]

The exact incidence of AKI caused by this herb is not known. Initial symptoms include convulsions, abdominal pain, diarrhea, and vomiting, which may be followed by stupor or coma and jaundice. Symptoms appear within a day in 40%, and within 4 days in more than two thirds of patients. Symptoms appear earlier and are more severe at extremes of age.[43-45] Severe hypoglycemia is observed in about 95%, metabolic acidosis in 87%, and renal failure in about 60% of cases.[46] Renal failure usually is oliguric and precedes hepatic dysfunction. The oliguric phase lasts 8 to 12 days. Renal histology shows acute tubular necrosis with interstitial edema and occasionally dense interstitial infiltration with lymphomononuclear cells.[47]

The precise mechanism of injury is not clear. The toxic principle is believed to be atractyloside, an alkaloid in the tuber of the plant. It inhibits the movement of adenosine diphosphate across the mitochondrial membrane, preventing the synthesis of adenosine triphosphate and causing cell death.[48] Volume depletion secondary to the gastrointestinal fluid loss also contributes to the kidney injury. Atractyloside can be detected in the herbal medicine, urine, or gastric lavage fluid with the help of thin-layer chromatography, gas chromatography-mass spectrometry, or high-performance liquid chromatography–mass spectrometry (HPLC-MS).[46]

Treatment is supportive and includes volume replacement and correction of hypoglycemia and dyselectrolytemia. The mortality rate is more than 50%.

Cape Aloe

Cape aloe is a herbal remedy that is used extensively in South Africa and generally is not considered to be toxic. In addition to its potent laxative effects, it is used for hypertension, eczema, arthritis, and stress. AKI is encountered regularly in those using remedies containing aloe in powder or extract forms. Toxic species include *Aloe capensis, A chabaudii, A excelsa, A greahheadii, A globuligemma*, and *A ferox Miller*. The active compounds are aloin and aloinosides. At one time it was suggested that most cases of ARF in South Africa were caused by remedies containing aloe extract or aloin, but the small number of cases relative to the reported amount of aloe medication use suggests that other mechanisms may be involved.[10] Patients with poisoning present with abdominal pain, bloody diarrhea, dehydration, and dyselectrolytemia. A lethal dose varies between 8 and 20 g.[49] Autopsy studies have revealed hemorrhagic gastroenteritis and acute tubular necrosis (ATN), suggesting that renal injury is secondary to dehydration.[50] Intravenous administration of Cape aloe has been associated with interstitial nephritis. Toxins may be detected using HPLC-MS with electrospray ionization. Treatment is supportive with appropriate fluid and electrolyte supplementation and dialytic support when required.

Djenkol Bean Poisoning

The djenkol (jering) trees (*Pithecolobium lobatum* and *Pithecolobium jiringa*, from the Mimosaceae family) grow widely in southeast Asian countries including Indonesia, Malaysia, southern Thailand, and Myanmar. The fruit takes the form of a bean and is considered a delicacy. The beans are consumed raw, fried, or roasted, and, less commonly, as sprouts. Poisoning can occur if they are consumed in large amounts, especially if eaten raw and associated with a low fluid intake.[51-55] It has been suggested that renal injury can be prevented by boiling, frying, or roasting the beans, or by cutting them up into

thin slices. However, frying does not necessarily protect from ARF.[55]

Toxic manifestations may appear soon after ingestion to as late as 36 hours after consumption and include dysuria, lumbar and lower abdominal pain, hypertension, hematuria, and oligoanuria.[54-56] Collectively, the symptom complex has been designated *djenkolism*. Kidney injury is most frequent in the rainy season, and there is a 9:1 male preponderance. In one large series,[52] dysuria (77%) and hematuria (68%) were the most frequent symptoms. About one third of patients showed hypertension and proteinuria and renal failure was detected in 45% and 55% of cases, respectively. Other manifestations include low-grade fever and leukocytosis. The breath and urine of patients emit a characteristic sulfuric odor.

The bean contains djenkolic acid ($C_{11}H_{23}N_3S_3O_6$), a sulfur-rich cysteine thioacetal of formaldehyde. It forms needle-like crystals at high concentrations and a low pH. They can precipitate and obstruct the distal tubules, ureters, and the urethra. The crystal may act as a nidus for stone formation, and chronic ingestion can lead to the development of djenkolic acid stones.[57,58] Renal histology of this condition, however, has not been well documented. Of the 2 case reports in which histology was available, one showed ATN and no abnormality was seen in the other. There is a possibility that crystals may have been dissolved during tissue processing. In animal experiments, ATN has been the predominant lesion, with some animals showing crystals.[59] Djenkolic acid infusion decreased the glomerular filtration rate and renal plasma flow in a dose-dependent fashion in experimental animals.[5]

Individuals vary greatly in their susceptibility to the toxic effects of this bean. Although even the ingestion of a single bean can be toxic for some individuals, it may take 20 beans or more to cause poisoning in others, and a few completely escape any adverse effect. Toxicity may be seen in only a few members of a large family, all of whom have consumed the beans. Some individuals, who have developed symptoms after the first meal, have been reported to have consumed the fruit later without any ill effects, whereas djenkolism also has been reported after many symptom-free meals in others. The reason for this variability may include differences in the hydration status related to changing temperature and humidity of the tropical climate, variations in activity of enzymes responsible for metabolizing the toxic product, and the difference in the djenkolic acid content among beans from various sources.[5] Urinalysis shows proteinuria and isomorphic hematuria. Needle-like crystals of djenkolic acid may be observed in fresh urine specimens under a phase-contrast microscope.

Management includes high fluid intake and urinary alkalinization to dissolve the crystals. Irrigation of the bladder or renal pelvis with alkaline solution has been advocated if the crystals are impacted in the lower urinary tract.[60] It has been suggested that djenkolism may be prevented by pretreatment of the beans by boiling or consumption of small amounts of the raw beans with liberal fluid intake.[60] With appropriate management, most victims recover within 2 weeks.

Mushroom Poisoning

Less than 1% of all mushrooms in the world are toxic. AKI has been reported after the ingestion of mushrooms of the genera *Amanita, Galerina, Cortinarius*, and *Inocybe*.[61-63] *Amanita phalloides* (death cap) and *Amanita virosa* (destroying angel), grow commonly in lawns, pastures, forests, on stumps, living trees, and in such unusual locations as basements, plaster board walls, and flower pots, and may be picked and ingested by inexperienced collectors and children in the mistaken belief that they are edible. This mushroom is recognized by its metallic green cap (the color may vary from light yellow to greenish brown), white gills (located under the cap), white stem, and bulb-shaped structure at the base of the stem. A pure white variety of this species also exists. There are certain folklores about differentiating poisonous from edible mushrooms. These are as follows: (1) a clove of garlic or a silver object turns black when cooked with a poisonous mushroom, (2) removal of the skin from the cap of a poisonous mushroom will make it edible, and (3) mushrooms that animals eat are

safe for human beings.[5] These beliefs have no basis in fact and should be ignored.

Poisoning can occur after ingestion of even one mushroom.[64] Toxic manifestations pass through 3 phases: the first phase (6-24 h) is dominated by gastrointestinal symptoms (abdominal cramping, nausea, vomiting, and severe watery diarrhea), which may lead to dehydration and hypotension. This is followed by a period of remission lasting 1 to 2 days. In the third phase, hepatic and renal failure, along with fever and alteration in consciousness, become manifest, which may lead to either death within the week or recovery in 2 to 3 weeks.[65-67] Jaundice is caused by hepatocellular failure. Renal failure usually is oliguric. The histology is compatible with ATN, with degenerative changes localized mainly to the proximal tubules; interstitial edema and cellular infiltration are encountered less frequently. The mortality rate is high (>50%) in the tropics,[68] and exceeds 70% in the pediatric population. The recovery from renal failure may not be complete. Long-term ingestion of *Cortinarious* mushrooms has been implicated in some cases of chronic renal failure.[69,70]

Cyclopeptides are the toxic agents and consist of two groups of molecules: phallotoxins and amatoxins. The latter inhibit RNA polymerases causing fragmentation and segregation of nuclear components, leading to hepatocellular and renal tubular necrosis. Amatoxins can be detected in the serum, plasma, or urine of the patient by using reverse-phase HPLC, HPLC-MS, or radioimmunoassay. Because of the rapid clearance rate, amatoxins are detectable in plasma for only up to 36 hours after ingestion, but can be detected in the urine for 4 days.[71] *Cortinarius orellanus* leads to a decrease in glomerular filtration rate, proteinuria, glycosuria, and decreased tubular reabsorption of sodium, potassium, and water within 48 hours in rats.[72] The toxic compound is orellanine and can be detected by thin-layer chromatography or electrophoresis. The toxic glycoprotein of *Boletus satanas* inhibits protein and DNA synthesis of Madine Darby canine kidney cells.[73] Volume depletion and hepatic failure also contribute to the renal injury.

Management is supportive; dialysis is given according to standard indications. Charcoal hemoperfusion is effective in clearing alfa-amanitin from circulation, and is thought to improve outcome.[74]

Propolis

Propolis, a resinous substance collected by honeybees, is used in hive construction and maintenance. It is claimed to possess antiseptic, antimycotic, bacteriostatic, astringent, choleric, spasmolytic, anti-inflammatory, anesthetic, antioxidative, hepatoprotective, and antitumor properties,[75-78] and has been applied in folk medicine since 300 BC in various parts of the world, particularly South America. Although there are numerous reports of allergic reactions, major systemic toxicity with propolis is uncommon. In a recent report, a 59-year-old man taking propolis for its antitumor activity developed oliguric acute renal failure requiring dialysis.[79] His renal function recovered after he stopped using propolis. However, the patient restarted it and again developed oliguria and renal failure, which recovered again after he stopped using propolis. The component of propolis inducing AKI remains unknown. The composition of propolis depends on time, vegetation, and the collection area.[80] More than 300 substances have been identified in propolis.[81,82] Chemical analysis of propolis extracts revealed high concentrations of aromatic acids, esters, and other derivatives, such as flavonoids, benzyl cinnamate, methyl cinnamate, caffeic acid, cinnamyl cinnamate, and cinnamoylglycine.[83] Therefore, it is hard to pinpoint the compound that causes AKI. Furthermore, there is a distinct possibility of contamination by other toxic agents during the processes of extraction, manufacture, and storage of propolis that can cause AKI.

Cat's Claw

Cat's claw or *uno degatta* is a Peruvian herbal preparation made from Unicarra, a woody vine found in the Amazon basin. It has been used to treat cirrhosis, gastritis, gonorrhea, and genital tract cancers; as an anti-inflammatory drug for rheumatism and systemic lupus erythematosus; as a contraceptive; and to cleanse the kidneys. Acute renal failure after the use of this preparation has been reported.[84] Renal biopsy shows acute interstitial nephritis and the renal failure

reversed after withdrawal of the agent. The acute interstitial nephritis (AIN) is likely an idiosyncratic allergic reaction to the remedy.

AKI After Use of Natural Medicines From Animal Sources

Although a majority of natural medicines are of botanical origin, in some areas they are derived from animal sources. Some examples are described.

Raw Carp Bile

Various kinds of fish traditionally are used for medicinal purposes in parts of Asia. The raw gallbladder or bile of freshwater and grass carps (*Ctenophryngodon idellus, Cyprinus carpio, Hypophythalmichthys molitrix, Mylopharyngodon pisceus*, and *Aristichthys nobilis*) are used as an antipyretic, antitussive, antihypertensive, and to improve visual acuity, rheumatism, and general health in rural areas of Taiwan, South China, Hong Kong, Japan, South Korea, and parts of India.[85-87] A syndrome of acute hepatic and renal failure has been reported from these countries and from the United States among immigrants after consumption of the gallbladder of these fish.[85-94]

Symptoms appear minutes to hours after ingestion and include abdominal pain, nausea, vomiting, and watery diarrhea. Hepatocellular jaundice is observed in more than 60% of patients. Renal failure sets in within 48 hours, and is oliguric in a majority. More than 75% also show microscopic hematuria.[85] The duration of renal failure ranges from 2 to 3 weeks. Reports from Taiwan highlight the absence of jaundice and dominance of depressed sensorium.[89,90] The variation in symptomatology likely is related to differences in the varieties of fish, amount of bile ingested, and individual susceptibility. There is an association between the size of the fish and the toxicity, and it has been suggested that ingestion of fish weighing less than 3 kg produces only minor symptoms. Renal histology reveals tubular necrosis and interstitial edema.

The mechanism by which ARF develops is not well understood, and may include bradycardia and hypotension owing to the cardiotoxic effect of the bile salts.[85] Bile salts also inhibit the intestinal Na-K–adenosine triphosphatase, which increases the mucosal permeability, leading to diarrhea. Bile produces diuresis, excessive salt loss, and cardiac depression in rats. Hypotension and hemolysis also may contribute to renal failure. Studies aimed at isolating the toxic compound found the activity in ethanol soluble and ether-insoluble fractions of the bile.[95] Cyprinol, a C-27 cholesterol–derived bile alcohol, has direct nephrotoxic properties.[96] In an experimental study, oral administration of freeze-dried grass carp bile juice powder, 5-alpha cyprinol, and 5-alpha cyprinol sulfate produced structural and functional abnormalities in the kidneys of Wistar rats.[97]

The prognosis of AKI is variable. Recovery has been universal among patients who have sought medical attention in a timely manner, and mortality has been limited to those who have reported their symptoms late and had multi-organ failure.[85]

Sheep Bile

The practice of ingestion of sheep bile for treatment for diabetes on the advice of local faith healers is prevalent among rural areas of Saudi Arabia. Epidemiologic studies have suggested that ingestion of 15 to 30 mL of the bile for 1 to 7 days was associated universally with nausea, vomiting, and diarrhea. Most patients experienced an acute decline in kidney function as reflected by an increase in serum creatinine level, along with a decline in serum sodium level. Oliguria and coma were noted in about 7% of patients.[98] The severity of the symptomatology was related directly to the dose of ingested bile, and returned to baseline after a fortnight. After this initial finding, reporting of such incidents was made mandatory by the Ministry of Health, and no reports have appeared subsequently in the literature.

In addition to the specific entities discussed earlier, there are some less frequently reported cases of natural medicine–induced AKI. Most of these cases are being reported as case reports and are summarized in Table 1.

In summary, the use of natural medicines is rampant in many parts of the world, mostly in impoverished areas with limited access to modern health care. People depend on faith healers

Table 1. Less Frequently Reported Natural Medicine–Induced AKI

Plant	Reported From	Active Molecule	Nature of Kidney Injury	Other Manifestations
Rhizoma rhei[99]	Hong Kong	Anthraquinones (emodin, aloe-emodin)	Acute interstitial nephritis	None
Catha edulis (khat leaf)[100–102]	East Africa, Arab peninsula	S-cathione, ephedrine	Acute tubular necrosis	Hepatotoxicity
Dioscorea quartiniana (yam)[55,103]	Africa, Asia	Discorine, dioscine	Acute tubular necrosis	Convulsions
Glycerrhiza glabrata (licorice)[104–106]	Japan	Glycerrhizic acid	Acute tubular necrosis	Rhabdomyolysis, hypokalemia, hypertension, cardiac arrhythmia
Larrea tridentate (chapparal)[107,108]	Chile, South Africa	Nordihydroguiaretic acid, s-quinone	Renal cysts, renal cell carcinoma	Hepatic failure
Securidacea longepedunculata (violet tree, wild wisteria)[109]	Congo	Methylsalicylate, securinine, saponins	Acute tubular necrosis	Vomiting, diarrhea
Spanish fly[110,111]	South Africa, United States	Cantharidin	Acute tubular necrosis, hematuria	Gastrointestinal symptoms, neuromuscular paralysis
Cleistanthus collinus (oduvan)[112–115]	India	Cleistanthin A and B, collinusin, diphyllin	Acute renal failure	Hypotension, hypokalemia, arrhythmia
Artemisia absinthium (wormwood essential oil)[116]	United States	Thujone, other volatile components	Acute renal failure	Tonic-clonic seizures, rhabdomyolysis
CKLS[117]	Atlanta, GA	Multiple toxins	Acute tubulointerstitial nephritis, hematuria	Diarrhea, abdominal pain
Tripterygium wilfordii (hook F)[118]	Taiwan	Triptolide	Acute tubular necrosis	Diarrhea, shock
Cupressus funebris Endl (mourning cypress)[119]	Taiwan	Flavonoid	Acute tubular necrosis, Interstitial nephritis	Acute hepatic failure, hemolytic anemia, thrombocytopenia
Colchicum autumnale (meadow saffron)[120]	Turkey	Colchicine	Acute tubular necrosis	Hemorrhagic gastroenteritis, muscle paralysis, respiratory failure
Sutherlandia frufesces (cancer brush), *Dodonaea angustifolia*[121]	South Africa	Unknown	Acute interstitial nephritis	Pulmonary embolism
Other plants[50]*				

CKLS, colon, kidney, liver, spleen; mixture of 10 plant products, the exact toxic compound is not known.
**Euphorbia metabelensis Crotalaria labminifolia Mentha pulegium.*

and witch doctors for supplies. The medicines are derived from botanical and less commonly from animal sources and are prepared in a crude fashion. Substitutions of plants and even contamination with chemicals often occur. AKI is one of the most frequent manifestations of toxicity and may be associated with involvement of other organs. The renal lesions include acute tubular necrosis, cortical necrosis, and interstitial nephritis. The prognosis depends on the severity of illness and the timeliness of presentation to hospitals. Poisoning also is encountered in the developed world among immigrants who continue to follow their rituals and among people who use these herbs in the form of dietary supplements. The study of natural medicine–induced AKI is difficult because of the mystery and secrecy surrounding it. The diagnosis may be missed if the history is not sought specifically. Awareness of this condition among nephrologists and physicians is important for appropriate diagnosis and management, and to eradicate this entity from the community.

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