A Review of Dietary Supplement–Induced Renal Dysfunction

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Complementary and alternative medicine (CAM) is a multibillion-dollar industry. Almost half of the American population uses some form of CAM, with many using them in addition to prescription medications. Most patients fail to inform their health care providers of their CAM use, and physicians rarely inquire. Annually, thousands of dietary supplement–induced adverse events are reported to Poison Control Centers nationwide. CAM manufacturers are not responsible for proving safety and efficacy, because the Food and Drug Administration does not regulate them. However, concern exists surrounding the safety of CAM. A literature search using MEDLINE and EMBASE was undertaken to explore the impact of CAM on renal function. English-language studies and case reports were selected for inclusion but were limited to those that consisted of human subjects, both adult and pediatric. This review provides details on dietary supplements that have been associated with renal dysfunction and focuses on 17 dietary supplements that have been associated with direct renal injury, CAM-induced immune-mediated nephrotoxicity, nephrolithiasis, rhabdomyolysis with acute renal injury, and hepatorenal syndrome. It is concluded that it is imperative that use of dietary supplements be monitored closely in all patients. Health care practitioners must take an active role in identifying patients who are using CAM and provide appropriate patient education.

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The use of complementary and alternative medicine (CAM) is commonplace in the United States (1). In a 2002 survey, 36% of Americans used some form of CAM, mostly herbs, nonherbal supplements, and vitamins (collectively referred to as dietary supplements) (2–4). In general, most CAM consumers are not dissatisfied with conventional medicine but instead are aiming to complement mainstream medicine (5). This attitude may be the result of patients' attempting to take responsibility for their own well-being, the perception that "natural" products are harmless, or simply a testament to the ease of CAM accessibility (2).

Only 12% of CAM users have sought care from a physician or licensed CAM practitioner, which suggests that most people use CAM without consulting a health care provider (2,4). This is significant because nearly 15 million dietary supplement users also use prescription medications (2). This dilemma may be attributed to the lack of specific questioning by practitioners or the patient's perception that the medical establishment has a negative attitude toward CAM. Forty-six percent of supplements users consider these products to be safe and effective. Unfortunately, most patients likely do not comprehend the potential for adverse events or drug–supplement interactions (2). The prevalence of drug misadventures related to CAM use is high. In 2003, nearly 25,000 CAM-related events were reported to the American Association of Poison Control Centers (6).

The Dietary Supplement Health and Education Act (DSHEA) of 1994 states that dietary supplements are not required to undergo premarket safety and efficacy testing (7). Also, there are no requirements for product labeling to warn of known or potential adverse reactions (8). As a whole, the lack of enforcement of good manufacturing practices in the dietary supplement industry is evident in reports of impurities and adulteration (9–11).

Drug-induced nephrotoxicity accounts for approximately 7% of all medication-related toxicities; therefore, it is reasonable to expect that some CAM may be nephrotoxic (12,13). However, the availability of dietary supplement–induced adverse reaction data is limited, because reporting of these events is voluntary (14). The majority of available information comes from case reports; therefore, tangible cause-and-effect relationships usually cannot be established. The objective of this article is to compile and briefly review the available data on CAM-induced nephrotoxicity. We provide detail of the renal injury and postulated mechanism of toxicity but are often limited by the data presented by the authors of the case reports. This review focuses only on supplements that commonly are available in the US market (Table 1). A variety of foods that are ingested for medicinal purposes have been associated with nephrotoxicity. A discussion of these medicinal foodstuffs (*e.g.*, star fruit, Jehring-fruit, Djenkol beans, Cape aloes) and their risk for nephrotoxicity is beyond the scope of this article. It should be noted that many widely used dietary supplements are not generally

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Table 1. Review of nephrotoxic dietary supplements[a]

Common Name	Familiar Indications	Nephrotoxic Manifestations
Cat's claw	Anti-inflammatory GI disorder	Acute allergic interstitial nephritis (43)
Chaparral	Antibiotic Anti-inflammatory Antioxidant	Renal cystic disease and low-grade cystic renal cell carcinoma (34)
Chromium	Glucose control Lipid lowering Weight loss	ATN (15,17) Interstitial nephritis (16)
Cranberry	Antibiotic Urinary acidifier and deodorizer	Nephrolithiasis secondary to oxaluria (58)
Creatine	Enhancement of muscle performance during brief, high-intensity exercise	Acute focal interstitial nephritis and focal tubular injury (18) Nonspecific renal dysfunction (19) AKI secondary to rhabdomyolysis (61–63)
Ephedra	Allergic rhinitis Asthma Hypotension Sexual arousal Weight loss	Nephrolithiasis secondary to ephedrine, norephedrine, and pseudoephedrine stone formation (55,56)
Germanium	Anti-inflammatory Immunostimulant	Tubular degeneration with minor glomerular abnormalities (23–32)
Hydrazine	Anorexia and cachexia Chemotherapeutic	Autolysis of the kidneys in the setting of hepatorenal syndrome (40)
Licorice	Antibiotic Anti-inflammatory GI disorders	Renal tubular injury secondary to prolonged hypokalemia (64–66) AKI secondary to hypokalemic rhabdomyolysis in the setting of pseudoaldosteronism (65)
L-Lysine	Antiviral Wound healing	Fanconi syndrome and tubulointerstitial nephritis (33)
Pennyroyal	Abortifacient Menstrual stimulant	Edematous hemorrhagic kidneys with ATN and proximal tubular degeneration in the setting of hepatorenal syndrome (69,71)
Thunder god vine	Immunosuppressant	Unknown supplement effects in conjunction with prolonged shock (42)
Vitamin C	Enhance iron absorption Prevention of cancer and heart disease Wound healing	Nephrolithiasis secondary to oxaluria (45–53)
Willow bark	Analgesic Anti-inflammatory	Necrotic papillae consistent with analgesic nephropathy (41)
Wormwood oil	Anemia Antipyretic Appetite stimulant Asthma GI disorders	AKI secondary to rhabdomyolysis in the setting of supplement-induced tonic-clonic seizures (60)
Yellow oleander	Anti-inflammatory	Renal tubular necrosis with vacuolated areas in the glomerular spaces in the setting of hepatorenal syndrome (73)
Yohimbe	Erectile dysfunction Sexual arousal	SLE with resultant renal dysfunction (37)

[a]AKI, acute kidney injury; ATN, acute tubular necrosis; GI, gastrointestinal; SLE, systemic lupus erythematosus.

taken in pure form but are mixtures of a variety of entities, which may have multiple interactions with each other. This makes it more difficult to identify the offending nephrotoxin in patients who consume CAM.

Direct Nephrotoxicity/Immune-Mediated Nephrotoxicity

Chromium Picolinate

There are three case reports of renal dysfunction secondary to chromium picolinate (CP) (15–17). The first patient had a 5-mo history of ingesting 1200 to 2400 μg/d CP and presented with anemia, hemolysis, thrombocytopenia, hepatic dysfunction, and acute kidney injury (AKI) (15). Chromium levels were three times normal. An abdominal ultrasound revealed enlarged kidneys, with muddy brown casts and urine microscopy consistent with acute tubular necrosis (ATN). No biopsy was performed. The patient's renal function improved after several days of hemodialysis (HD) (15). A second case of ATN was seen in a 24-yr-old man who presented with AKI after a 2-wk history of consuming a supplement that contained CP (17). A computed tomography scan and an abdominal ultrasound showed inflammation in the right, sole kidney. A renal biopsy revealed

necrotic tubular epithelium with intraluminal debris consistent with ATN. The patient was treated with HD, plasmapheresis, and corticosteroids and ultimately regained normal renal function (17). Another patient ingested 600 μg/d CP for 6 wk and presented 5 mo later with severe renal dysfunction (16). A renal biopsy revealed severe chronic active interstitial nephritis, consistent with heavy-metal exposure. Renal function improved with corticosteroid therapy (16).

Creatine Monohydrate

Controversy surrounds the potential of creatine to induce renal failure. Several small-scale trials argued against creatine-induced nephrotoxicity, although creatine has been associated with two cases of renal dysfunction (18–22). Koshy *et al.* (18) described a 20-yr-old man with a 4-d history of nausea, vomiting, and bilateral flank pain that commenced 4-wk after consuming 5 g/d creatine. Laboratory analysis revealed an elevated serum creatinine (SCr). Urinalysis showed proteinuria and hematuria, with urine sediment containing white-cell casts and dysmorphic red cells. A renal biopsy demonstrated acute focal interstitial nephritis, tubular injury, a thickened basement membrane, and effacement of the foot processes. Renal function fully recovered after hydration (18). The second case involved a 25-yr-old man with an 8-yr history of FSGS and frequently relapsing nephrotic syndrome (19). The patient had been in remission for 5 yr. After consuming induction (15 g/d for 1 wk) and maintenance (2 g/d for 12 wk) dosages of creatine, the patient's SCr increased and GFR decreased significantly, although a biopsy was not done. One month after stopping the creatine, the patient's renal function normalized (19).

Germanium

Germanium has been associated with renal dysfunction, and, in all cases, the overall exposure to germanium ranged from 2 to 36 mo and the cumulative dosage of germanium ingested ranged from 15 to 426 g. In most cases, histologic examination revealed tubular degeneration with minor glomerular abnormalities. Recovery of renal function is often slow and incomplete (23–32).

L-Lysine

L-Lysine has been reported to cause Fanconi syndrome and tubulointerstitial nephritis. Fanconi syndrome is impairment in renal proximal tubular function and may lead to acidosis, dehydration, and electrolyte imbalances. It is often treated supportively until the underlying cause is addressed. A single case report identified a 44-yr-old woman who developed Fanconi syndrome and tubulointerstitial nephritis after consuming 3000 mg/d L-lysine for 5 yr. Subsequently, the patient progressed to chronic renal failure (33).

Larrea tridentate (Chaparral)

Chaparral-induced nephrotoxicity is reported in a single case involving a 56-yr-old woman with a 3-mo history of chaparral ingestion 18 mo before diagnosis (34). The patient presented with an elevated SCr and was found to have bilateral renal cystic disease and cystic renal cell carcinoma (34). Meticulous search excluded major causes of cystic renal disease. The authors concluded that nordihydroguaiaretic acid, in the form of chaparral, was the most likely cause of the carcinoma. Nordihydroguaiaretic acid is a major constituent of chaparral and has been associated with cystic nephropathy in animal studies (35,36).

Pausinystalia yohimbe (Yohimbe)

Progressive renal failure and proteinuria is reported in a 42-yr-old man who also developed generalized erythrodermic skin eruptions, fever, and pleural and pericardial effusions 1 d after taking yohimbine, a component of yohimbe. A renal biopsy was not preformed in this case. The patient was treated with corticosteroids and regained normal renal function within 2 wk. The authors concluded that this was yohimbine-induced systemic lupus erythematosus with resultant renal dysfunction (37).

Salix daphnoides (Willow Bark)

The active constituent of willow bark is believed to be salicin. *In vivo*, salicin is metabolized to saligenin, which is further metabolized to salicylate (38,39). Salicylates are known to cause renal dysfunction, secondary to prostaglandin inhibition and a reduction in renal blood flow (40). Willow bark has been implicated in the renal dysfunction diagnosed on review of the autopsy of Ludwig van Beethoven (41). His kidneys were described as normal size and shape but with calcareous deposits in each calyx. It is believed that these deposits were necrotic papillae consistent with analgesic nephropathy (40,41).

Tripterygium wilfordii hook F (Thunder God Vine)

A single case report of renal and cardiac toxicity in a 36-yr-old man has been reported (42). Three days after ingesting thunder god vine extract, the patient presented with profuse nausea, vomiting, diarrhea, leukopenia, renal failure, hypotension, and extensive cardiac abnormalities. The patient died 3 d after presentation from intractable shock. The authors could not differentiate the cause of this patient's renal dysfunction, postulating that it could have been supplement-induced nephrotoxicity, in conjunction with prolonged shock (42).

Uncaria tomentosa (Cat's Claw)

A case report of cat's claw–induced renal dysfunction described a patient who had systemic lupus erythematosus and worsening renal function and urinary sediment abnormalities after using cat's claw (43). A biopsy was not done, but a diagnosis of acute allergic interstitial nephritis was made. Renal function improved 1 mo after discontinuation of the supplement (43).

Nephrolithiasis

Stone formation within the urinary tract represents a complication of several disease states. Renal stones are generally composed of calcium, oxalate, urate, cystine, or struvite. However, the exact composition of the stones depends on the underlying condition. Kidney stones travel through the collecting system, but many are too large to negotiate the narrow conduits, causing obstruction with resultant renal dysfunction.

Ascorbic Acid (Vitamin C)
Vitamin C is metabolized to several byproducts, including oxalate, before elimination *via* filtration and tubular reabsorption (44). Multiple episodes of oxalosis from vitamin C supplementation have been reported (45–53). In all cases, the administration of high-dosage vitamin C (nearly 60 g/d) resulted in extensive oxalate deposition in the renal tubules with associated ATN. These cases of renal failure improved after HD and/or supportive care (45–53).

Ephedra sinica (Ephedra, Ma-Huang)
Since 1994, the Food and Drug Administration has received nearly 1000 reports of ephedra-induced adverse events (54). There have been two reports of nephrolithiasis associated with ephedra. Both patients were male young adults with a history of ingesting 40 to 3000 mg/d ephedra over several months (55,56). Analysis of the stones revealed the presence of ephedrine, norephedrine, and pseudoephedrine. The Food and Drug Administration has determined that ephedra presents an unreasonable risk for adverse events, and in April 2004, it prohibited the sale of ephedra-containing dietary supplements in the United States (57). Despite this ban, ephedra is widely available for purchase on the internet.

Vaccinium macrocarpon (Cranberry)
Cranberries contain oxalate, and one concentrated cranberry tablet (450 mg) contains approximately 180 mg of oxalate. Terris *et al.* (58) described a 47-yr-old man with nephrolithiasis secondary to daily consumption of cranberry tablets for 6 mo. After presenting with severe right flank pain, hematuria, and an elevated SCr, an abdominal ultrasound revealed left and right ureteral stones. The patient's SCr normalized after stone removal. Calcium oxalate was present in the stones. After reviewing this patient's case, the authors conducted an experiment to analyze 24-h urine samples from five healthy volunteers before and after consumption of cranberry. Oxalate excretion increased 43.4% after cranberry ingestion. The authors concluded that concentrated cranberry tablets increase the risk for calcium-oxalate stone formation (58).

Rhabdomyolysis

Rhabdomyolysis may be asymptomatic or present with muscle weakness or myalgias and creatinine phosphokinase (CPK) elevations. More severe cases may include electrolyte imbalances and AKI. Rhabdomyolysis can be caused by trauma, extreme physical exertion, electrolyte imbalances, or certain medications (59). Reports of CAM-induced acute rhabdomyolysis leading to renal dysfunction are reviewed next.

Artemisia absinthium (Wormwood Oil)
Weisbord *et al.* (60) described a 31-yr-old man with AKI secondary to ingestion of wormwood oil. After consuming 10 ml of oil, the patient developed tonic-clonic seizures. The patient reported bilateral muscle soreness in his legs on hospital day 2 and reached his peak SCr on hospital day 3. With supportive care, the patient's renal function normalized 17 d after presentation (60). The authors concluded that wormwood oil was responsible for the patient's seizure, which apparently led to rhabdomyolysis and subsequent AKI. Although this is not a case of direct supplement-induced rhabdomyolysis, it does outline the importance of CAM-induced adverse events. Table 2 contains a group of dietary supplements that have been associated with seizures in humans.

Creatine Monohydrate
Five cases of AKI secondary to exercise-induced rhabdomyolysis have been described in young men who took performance-enhancing supplements that included creatine (5 to 25 g/d) (61–63). All patients developed extreme muscle pain after participating in strenuous exercise and developed severe rhabdomyolysis. Three patients required HD, four developed compartment syndrome necessitating fasciotomy, and one died of multisystem organ failure (61–63).

Glycyrrhiza glabra (Licorice)
Licorice is a potent diuretic and has been associated with severe hypokalemia (39,64). Renal failure is a rare adverse event associated with licorice, but reports of nephrotoxicity secondary to hypokalemia have been described. In one case, a 78-yr-old man, who consumed 280 mg/d of licorice for 7 yr, was hospitalized for muscle pain and AKI (65). Initial laboratory analysis noted hypokalemia with elevated CPK and myoglobin levels. AKI and profound calcium deposition seen in the muscles were secondary to licorice-induced hypokalemic rhabdomyolysis (65). Another case described a 29-yr-old woman who consumed 30 licorice tablets per day for 4 mo to promote weight loss (66). The patient developed painful muscle weakness and was found to have hypokalemia and an elevated CPK. A renal biopsy revealed severely damaged tubular cells with intense vacuolar formations (66).

Licorice produces rhabdomyolysis-induced renal dysfunction as a result of potassium diuresis. Several other dietary supplements have been used for their diuretic-like effects, and these agents should be used with caution, especially in patients with underlying renal dysfunction or those who take prescription diuretics (67). A list of these agents can be found in Table 3.

Hepatorenal Syndrome

Hepatorenal syndrome is the development of AKI in patients with liver dysfunction. The development of renal dysfunction is an indicator of clinical deterioration as a result of decreased renal perfusion. Overall, increased perfusion requirements activate the renin-angiotensin-aldosterone system with resultant renal vasoconstriction. Treatment is centered on correcting the

Table 2. Dietary supplements (common names) associated with seizures (97)

Aspartamine	Kava kava
Bearberry	Monkshood
Black cohosh	Water-hemlock
Ephedra	Wormwood oil
Guarana	Yohimbe

Table 3. Dietary supplements (common names) with known or potential diuretic properties (39,67)

Aloe vera	Creatine	L-Arginine
Antineoplaston	Dandelion	Lovage
Artichoke	Elder flower	Meadowsweet
Asparagus	Ephedra	Mistletoe
Astragalus	Gingko	Oleander
Birch	Glucosamine	Shepherd's purse
Bladderwrack	Goldenrod	Sorrel
Bupleurum	Gotu kola	Uva ursi
Burdock	Green tea	White horehound
Copper	Horsetail	Yarrow flowers
Corn silk	Juniper berry	
Couch grass	Kava	

underlying hepatic dysfunction. Dietary supplements with documented hepatorenal syndrome are discussed next. However, many CAM are hepatotoxic but have yet to produce published reports of hepatorenal syndrome (67). Table 4 contains those CAM with reported hepatotoxic adverse events.

Hedeoma pulegioides (Pennyroyal)

Pennyroyal has been associated with renal dysfunction in the setting of hepatotoxicity (68,69). Two infants died of combined liver and renal failure after ingestion of preparations that contained pennyroyal (69,70). An autopsy in one of the children revealed hepatocellular necrosis, edematous hemorrhagic kidneys with ATN, left adrenal hemorrhage, and bilateral lung consolidation (69). Another report described a young woman who presented with oliguria and died within 48 h of multisystem organ failure and anoxic encephalopathy (71). Postmortem findings revealed acute proximal tubular degeneration.

Hydrazine Sulfate

A 55-yr-old man presented 2 wk after discontinuing hydrazine, 180 mg/d for 4 mo, with a rash, pruritus, malaise, and jaundice (72). Initial laboratory results revealed uremia and elevated liver function tests and prothrombin time. The patient subsequently developed hepatic encephalopathy, coagulopathy, and progressive renal failure, leading to the initiation of HD. Autopsy revealed autolysis of the kidneys. The authors noted that there was no evidence of metastatic disease or preexisting liver/kidney disease and that the AKI was likely secondary to hepatorenal syndrome (40). A similar case of multisystem organ failure was reported in a patient who handled hydrazine for industrial applications (72).

Table 4. Hepatotoxic dietary supplements (common names) (39,67)

Bee pollen	Coltsfoot	Mistletoe
Birch oil	Comfrey	Periwinkle
Blessed thistle	DHEA	Sassafras
Borage	Echinacea	Turmeric
Bush tea	Ephedra	Uva ursi
Butterbur	Germander	Valerian
Cascara Sagrada	Green tea	White chameleon
Celandine	Kava	
Chaparral	Lobelia	

Thevetia peruviana (Yellow Oleander)

Four cases of nephrotoxicity were seen in patients who consumed yellow oleander and consequently developed jaundice, oliguria, and fever (73). Serum bilirubin, SCr, and blood urea nitrogen levels all were elevated. One patient received HD and recovered after 1 mo. The other patients died of multisystem organ failure. Postmortem analysis revealed renal tubular necrosis with vacuolated areas in the glomerular spaces (73).

Adulterants

According to the DSHEA of 1994, adulteration of a dietary supplement occurs when supplements present a significant risk for inducing illness or injury when used as specified by product labeling, are a new entity and there are no data available to ensure its proper use, have been acknowledged by the Department of Health and Human Services as being harmful, or contain an ingredient that is capable of rendering the product deleterious to human health (7). On the basis of the DSHEA definition of adulteration, contamination (unintentional or intentional) is a form of adulteration.

Reports of contamination of dietary supplements are common. However, few cases of CAM adulteration have resulted in renal injury. Aristolochic acid is the most well-documented adulterant with nephrotoxic adverse events. Other common contaminants, such as the heavy metals (*e.g.*, arsenic, lead, mercury) and synthetic drugs (*e.g.*, indomethacin, ibuprofen, phenylbutazone, mefenamic acid), may also have nephrotoxic potential (74–78).

Aristolochic Acid

The correlation between nephrotoxicity and CAM use was brought to the forefront when case reports emerged of nine Belgian women who presented with rapidly progressing renal failure as a result of biopsy-proven tubulointerstitial nephritis. None of the women had any history of renal disease, but all had consumed the same weight-loss supplement. Chromatographic analysis of the supplement revealed that the preparation had been adulterated with *Aristolochia* (39). The primary constituent of *Aristolochia* is aristolochic acid. Several case reports have demonstrated the nephrotoxic properties of aristolochic acid, leading to what is called "Chinese herb nephropathy." The major renal injury is extensive interstitial fibrosis with tubular atrophy and loss (79). Some speculate that aristolochic acid may also be associated with Balkan endemic nephropathy, although a definite association remains unproved. In addition, exposure to aristolochic acid increases the risk for urothelial malignancies (79,80). In a series of 39 patients (31 posttransplantation; eight HD) who developed Chinese herb nephropathy and underwent the prophylactic removal of their nonfunctioning native kidneys and ureters, 18 cases of urothelial carcinoma were found (81). In 19 of the 21 patients without carcinoma, urothe-

Table 5. Dietary supplements with theoretic nephrotoxic potential (39)[a]

Potential Mechanism	CAM Scientific Name (Common Name)
COX inhibition (altered renal hemodynamics)	*Curcuma longa* (turmeric)
	Filipendula ulmaria (meadowsweet)
	Tanacetum parthenium (feverfew)
	Zingiber officinale (ginger)
	Boswellia serrata (frankincense)
	Camelia sinensis (green tea)
	Aesculus hippocastanum (horse chestnut)[b]
Nephrolithiasis	*Rheum officinale* (rhubarb)
	Rumex acetosa (sorrel)[c]
	Rumex crispus (yellow dock)
Rhabdomyolysis	*Cannabis sativa* (marijuana)[d]
	Colchicum autumnale (autumn crocus)
	Commiphora mukul (guggul)
	Coutarea latiflora (copalchi)
	Monascus purpureus (red yeast)

[a]CAM, complementary and alternative medicine; COX, cyclooxygenase.
[b]Case report of intravenous horse chestnut–induced nephrotoxicity, presumably secondary to vasoconstriction from a high aescin content (no reports linked to oral formulations, which have a much lower aescin content) (39).
[c]One case report of sorrel-induced nephrolithiasis when consumed as a foodstuff and not as a dietary supplement (98).
[d]Case report of rhabdomyolysis was with the use of intravenous marijuana (99).

lial lesions, resulting from mild to moderate dysplasia, were discovered. The authors concluded that cumulative exposure to >200 g of aristolochic acid significantly increased the risk for urothelial malignancies.

Heavy Metals

Contamination of dietary supplements with heavy metals is a common concern. Most often, supplements are contaminated with heavy metals as a result of growth or cultivation in contaminated areas. Heavy metals can cause significant renal damage. Arsenic affects the renal capillaries, tubules, and glomeruli, causing tubular necrosis and degeneration over time, yet detailed mechanisms are not well understood. Chronic lead exposure can affect a variety of organ systems, including the kidneys, where it produces a chronic interstitial nephritis. Mercury causes damage to the renal proximal tubule and heme-biosynthetic pathways (82,83). Concerns of CAM contamination with mercury (*e.g.*, fish oil, ephedra) and lead (*e.g.*, calcium supplements) have been dismissed after evaluations of several products (84–87), although there are some documented cases of renal toxicity that resulted from CAM products that were contaminated with heavy metals.

A single case of bladderwrack-induced nephrotoxicity has been reported; the renal injury was attributed to high levels of arsenic found within the bladderwrack (88). The presence of arsenic in kelp preparations is possibly a result of growth in contaminated water (88,89). This case involved a young woman who presented with polydipsia, polyuria, proteinuria, and AKI after taking 1200 mg/d bladderwrack for 3 mo. Renal biopsy revealed tubular degeneration and lymphomonocytic infiltration. One year after discontinuing the supplement, the patient's renal function normalized (88).

Synthetic Drugs

Numerous studies that have reviewed the purity of CAM preparations have found nonsteroidal anti-inflammatory drugs (NSAID), such as ibuprofen, phenylbutazone, and mefenamic acid, to be contaminants in products that are intended as analgesics or anti-inflammatories (76–78,90–93). The NSAID cause inhibition of renal prostaglandins, resulting in renal vasoconstriction and resultant ischemia. With long-term exposure, interstitial nephritis, nephritic syndrome, and papillary necrosis can occur (94,95). Nephrotoxicity as a results of NSAID adulteration is possibly seen in some cases involving glucosamine. Several cases of reversible renal dysfunction or mild proteinuria have been associated with the use of glucosamine-containing supplements. Unfortunately, the authors of these case reports provided few details of the exact renal injury. Many of the reporting authors concluded that the nephrotoxicity might have been due to concomitant medications or impurities/adulterants in the glucosamine preparations, although analysis of the products was never completed to confirm these conclusions (78,96).

Theoretic Potential to Induce Renal Dysfunction

Some CAM therapies that are not associated with renal dysfunction warrant discussion. The agents listed in Table 5 have the potential to be nephrotoxic because of their mechanisms or adverse event profile. The lack of evidence does not mean that

these CAM are safe, and renal function should be monitored in all patients who consume these agents.

Conclusion

Dietary supplements are a significant component of the over-the-counter market. Consumers generally view these products as safe and effective alternatives to conventional therapies, and most users include these products in their therapeutic regimens without consulting health care providers. Patients do not always comprehend the potential dangers of consuming these products. The current lack of supplement standardization further complicates CAM use. Additional information is needed regarding dietary supplement safety and efficacy, especially in the settings of underlying illness and concomitant prescription medication use.

Most relevant data on CAM-induced nephrotoxicity come from individual case reports, and it is often impossible to prove a definitive cause-and-effect relationship. These reports are not to be considered conclusive evidence. However, circumstantial evidence, in some cases, is strong and warrants caution. Dietary supplement use should be monitored closely in patients who have or at risk for renal dysfunction. It is imperative that health care practitioners take an active role in identifying CAM use among their patients, are aware of possible complications, report any drug misadventures, and educate their patients on the need for open communication regarding CAM.

Disclosures

None.

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