Nephrotoxicity of Natural Products

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Key Words

Natural products · Dietary supplements · Complementary and alternative medicine · Nephrotoxicity · Renal dysfunction

Abstract

Background: The manufacture and sale of natural products constitute a multi-billion dollar industry. Nearly a third of the American population admit to using some form of complementary or alternative medicine, with many using them in addition to prescription medications. Most patients fail to inform their healthcare providers of their natural product use and physicians rarely inquire. Annually, thousands of natural product-induced adverse events are reported to Poison Control Centers nationwide. Natural product manufacturers are not responsible for proving safety and efficacy, as the FDA does not regulate them. However, concerns exist surrounding the safety of natural products. **Summary:** This review provides details on natural products that have been associated with renal dysfunction. We have focused on products that have been associated with direct renal injury, immune-mediated nephrotoxicity, nephrolithiasis, rhabdomyolysis with acute renal injury, hepatorenal syndrome, and common adulterants or contaminants that are associated with renal dysfunction. **Key Messages:** The potential for natural products to cause renal dysfunction is justifiable. It is imperative that natural product use be monitored closely in all patients. Healthcare practitioners must play an active role in identifying patients using natural products and provide appropriate patient education.

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Introduction

The term complementary and alternative medicine (CAM) refers to any healthcare approach developed outside of mainstream (i.e. Western, conventional) medicine [1]. It is important to define CAM so that practitioners can accurately understand its practice and impact on patient care. 'Complementary' generally refers to using a non-mainstream approach together with conventional medicine; whereas 'alternative' refers to using a non-mainstream approach in place of conventional medicine. True alternative medicine is uncommon in the United States, as most CAM users utilize non-mainstream approaches in combination with conventional treatments. The boundaries between complementary and conventional medicine often overlap and are dynamic. Most complementary health approaches fall into one of 2 subgroups: natural products or mind and body practices [1]. This review focuses on natural products, which include herbs (i.e. botanicals), vitamins, minerals, and probiotics.

In the United States, the Dietary Supplement and Health Education Act (DSHEA) of 1994 was established to regulate natural products [2]. This act instituted that natural products are not required to undergo premarketing safety and efficacy testing. This is an important factor, as it helps distinguish between natural products and pre-

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scription/non-prescription medications. One result of the DSHEA is that natural products are marketed widely and readily available. However, this may lead to confusion and ultimately mislead consumers into believing that natural products are safe and effective and have undergone similar premarket testing as prescription and/or non-prescription medications. Natural products are also not required to include warnings of known or potential adverse events in product labeling. Another regulatory issue that surrounds natural products is the relative lack of enforcement of good manufacturing practices that have led to multiple reports of impurities, contamination and adulteration of dietary supplements, as well as several reports demonstrating that some natural products do not contain any of the ingredients listed on their labels [2, 3].

The global natural products market was valued at \$109.8 billion in 2013 and is expected to grow to reach an estimated value of \$179.8 billion in 2020 [4]. This demonstrates the increasing propensity for consumers to regularly consume natural products. A 2012 National Health Interview Survey showed that 33.2% of Americans used CAM approaches while managing their health [5]. In this survey, 17.7% of adults and 4.9% of children used non-vitamin, non-mineral natural products. The most commonly used natural products identified in this report included fish oil (omega-3 fatty acids), glucosamine (with or without chondroitin), probiotics/prebiotics, melatonin, coenzyme Q10, echinacea, cranberry, garlic, ginseng, ginkgo biloba, green tea extracts, and milk thistle. It was noted that only a minority of natural product users ever seek care from a physician or licensed CAM practitioner. This implies that most people utilize natural products without consulting a healthcare provider [5]. This is significant because nearly 15 million dietary supplement users also use prescription medication. Over 45% of natural product users consider these products to be safe and effective and perceive no potential for adverse events or drug interactions [6].

The toxicity profile of individual botanicals is usually not well established. This is the result of a lack of standardized adverse event reporting systems, as well as patients neglecting to report natural product use to their healthcare professionals. In its 2013 annual report, it was noted that 38,955 natural product-related exposures were reported to the American Association of Poison Control Centers [7]. Another complicating factor is that many natural products are not always marketed in their pure form, but instead in combination with a variety of other natural products. This makes it

very difficult to identify a cause-and-effect relationship between an individual natural product and specific toxicity.

Methods

We performed a Medline search for medical literature and case reports by using the following keywords: botanical, herbal, dietary supplement, CAM, natural products, nephrotoxicity and renal insufficiency/dysfunction/failure. We included human and clinical case reports of nephrotoxic events associated with the consumption of natural products. We focused on natural products that resulted in significant reductions in glomerular filtration rate, as evaluation of other nephrotoxic manifestations would be too encompassing and difficult to draw any firm conclusions from. One of our major inclusion criteria was that the natural products reviewed here had to be available in the United States, self-administrable (oral tablet, capsule, powder or liquid) and be easily purchased without a prescription (i.e. available in major chain retailers (in store and online) and pharmacies). The objective of this article is to compile and briefly review the data described in case reports and small studies of natural product-induced nephrotoxicity. The natural products have been sorted based on their proposed mechanism of nephrotoxicity, and include those that cause direct or immune-mediated nephrotoxicity, nephrolithiasis, rhabdomyolysis-induced renal dysfunction, hepatorenal syndrome, and adulterants/contaminants that have resulted in nephrotoxicity.

Direct or Immune-Mediated Nephrotoxicity

Given the excretory role of the kidneys, these organs are highly exposed to a large proportion of circulating xenobiotics. They have a large surface area and receive high blood flow, nearly 25% of cardiac output. As a consequence, they are highly susceptible to acute or chronic kidney injury by medicinal compounds. Patients with compromised renal function are at a higher risk for further deterioration of kidney function.

Nephrotoxicity from medications and/or natural products may manifest in many different ways, including acid-base disorders, electrolyte abnormalities, alterations in urine sediment, new onset proteinuria, pyuria or hematuria, and reduced glomerular filtration. Xenobiotic-induced acute kidney injury (AKI) accounts for approxi-

mately 20% of reported cases of AKI [8]. Given this statistic, it is reasonable to expect that some natural products may impact renal function.

Natural products that have a direct and/or immune-mediated nephrotoxic effect are discussed in table 1. The most common toxicities seen in these cases included direct tubule effects and interstitial nephritis. It is important to know that some products may affect renal function in more than one way. Most of the information reviewed comes from singular case reports; therefore, cause-and-effect relationships are difficult to establish.

One natural product that requires further discussion is creatine. There are 2 types of creatine products available in the United States: creatine ethyl ester and creatine monohydrate. Creatine ethyl ester is more readily converted into creatinine in the gastrointestinal tract. Use of creatine ethyl ester may be associated with elevated plasma creatinine levels due to increased oral absorption thereby, potentially resulting in a false presumption of renal dysfunction [9].

Nephrolithiasis

Kidney stones can form as a result of several factors, but most likely due to the accumulation of calcium, oxalate, uric acid, cystine or struvite. Several natural products have been associated with nephrolithiasis and their cases are discussed in table 1. The natural products rhubarb and yellow dock have been associated with nephrolithiasis when they have been consumed as foodstuffs, but not as dietary supplements [10]. Several other natural products have been theorized to increase the risk for kidney stone formation, but no case reports currently exist. These products include caffeine, calcium supplements, parsley leaf, skunk cabbage, and spinach leaf. Caffeine has been shown to increase calcium oxalate excretion, while parsley leaf, skunk cabbage and spinach leaf all contain high concentrations of oxalates [10].

Rhabdomyolysis

Rhabdomyolysis may be asymptomatic or present with muscle weakness or myalgias and elevated creatine phosphokinase levels [11]. It may be caused by trauma, extreme physical exertion, electrolyte imbalances, or certain medications. If left untreated, this may ultimately lead to electrolyte imbalances followed by AKI. Agents that have been associated with rhabdomyolysis-induced renal dys-

function are discussed in table 1. The natural products guggul and red yeast rice have been associated with rhabdomyolysis, but without documentation of AKI [10].

Hepatorenal Syndrome

Hepatorenal syndrome is one potential cause of AKI in patients with acute or chronic liver disease, where kidney injury is the result of reductions in renal perfusion induced by a severe hepatic injury [12]. Several natural products are associated with hepatotoxicity, with the most notable products including cascara sagrada, comfrey, DHEA, echinacea, ephedra, green tea, kava, mistletoe, turmeric, and valerian root [10]. Despite their ability to induce hepatotoxicity, there has been no documented report of progression to hepatorenal syndrome after taking any of these natural products. The dietary supplements associated with hepatorenal syndrome are detailed in table 1.

Adulterants and Contaminants

Adulteration of natural products occurs when supplements contain an ingredient that is capable of rendering the product deleterious to human health [1]. On the basis of this definition, contamination, either intentional or unintentional, is considered a form of adulteration. Natural products vary in their processing and manufacturing from identification, extraction and purification leading to various concentrations of the active ingredient from batch-to-batch. However, several natural products have been found to contain prescription medications or other medicinal compounds. Intentional adulteration is seen predominantly in natural products marketed for weight loss, sexual health, and athletic performance. However, few cases of natural product adulteration have resulted in renal injury. Some of the more common intentional adulterants include nonsteroidal anti-inflammatory drugs (NSAID) and diuretics. Natural products adulterated with NSAIDs, claiming efficacy as anti-inflammatories or antipyretics, can lead to renal vasoconstriction and possibly ischemia that consequently result in interstitial nephritis, nephritic syndrome, and papillary necrosis. Natural products adulterated with diuretics are often used as weight-loss supplements. Natural products with diuretic-like effects, or those adulterated with diuretics, may often result in some renal and/or electrolyte abnormalities. Reports of contamination of natural products are also com-

Table 1. Natural products with documented nephrotoxicity^{xii}

Natural product (n)	Dose	Renal manifestations	Management/outcomes
Direct or immune-mediated nephrotoxicity			
Bee pollen (n = 1) [17]	Daily dose unknown; ingested for over 5 months	AKI, including presence of eosinophils	HD and supportive care; renal dysfunction resolved
Bee propolis (n = 1) [18]	>1,400 mg/kg/day, ingested for over 2 weeks	AKI with AIN, hematuria, proteinuria, hyperkalemia and hyponatremia	HD and supportive care; renal dysfunction resolved
Chromium picotoline (n = 3) [19–21]	600–2,400 µg/day, ingested over 2 weeks to over 5 months	ATN with associated anemia and hemolysis	HD, PP and corticosteroids; renal dysfunction resolved
<i>Crataegus orientalis</i> (Hawthorn; n = 1) [22]	500 g/day; duration unknown	AKI with hematuria, proteinuria, hyperkalemia and metabolic acidosis	HD, corticosteroids and supportive care; renal dysfunction resolved
Creatine monohydrate (n = 2) [23, 24]	2–15 g/day, ingested over 1–12 weeks	Acute focal interstitial nephritis with tubular injury; thickened basement membrane; presence of proteinuria and hematuria	Hydration and supportive care; renal dysfunction resolved
Germanium (n = 10) [25–34]	Cumulative doses of 15–426 g, ingested over 2–36 months	Tubular degeneration. Patients also experienced gastrointestinal symptoms, pericarditis, liver and thyroid dysfunction, polyneuropathy and diabetes	Supportive care; renal dysfunction resolved but was often slow and incomplete
<i>Juniperus oxycedrus</i> (Juniper tar; n = 1) [35]	Daily dose and duration unknown	AKI with hematuria and proteinuria; cardiac and liver abnormalities	Hydration and supportive care; renal dysfunction resolved after 8 days
L-Lysine (n = 1) [36]	3 g/day, ingested for over 5 years	Fanconi syndrome, ATN, acidosis, dehydration and electrolyte abnormalities	Supportive care; renal function never recovered and the patient advanced to CKD
<i>Larrea tridentate</i> (Chapparal; n = 1) [37]	Daily dose and duration unknown	Bilateral renal cystic disease, cystic renal cell carcinoma	Not discussed
<i>Pausinystalia yohimbe</i> (Yohimbine; n = 1) [38]	Daily dose and duration unknown	Progressive renal failure with proteinuria. Patient also presented with generalized erythrodermic skin eruptions leading authors to conclude this was Yohimbine-induced SLE	Corticosteroids and supportive care; renal dysfunction resolved
<i>Salix daphnoides</i> (Willow bark; n = 1) [39]	Daily dose and duration unknown	Calcareous deposits in calyx with renal dysfunction likely secondary to prostaglandin inhibition	Not discussed
<i>Tripterygium wilfordii hook F</i> (Thunder god vine; n = 1) [40]	Daily dose and duration unknown	Nephropathy and renal dysfunction with cardiac abnormalities and hypotension	Supportive care; patient passed away secondary to these events
<i>Uncaria tomentosa</i> (Cat's claw; n = 1) [41]	Daily dose and duration unknown	Allergic AIN, with urinary sediment abnormalities	Hydration and supportive care; renal dysfunction resolved
Nephrolithiasis			
Ascorbic Acid (Vitamin C; n = 9) [42–50]	Daily doses of up to 60 g/day; duration unknown	Oxalate deposition in the renal tubules with associated nephrolithiasis and ATN	HD and/or supportive care; renal dysfunction resolved in all cases
<i>Ephedra sinica</i> (Ephedra, Ma-huang; n = 2) [51, 52]	40–3,000 mg/day for several months	Nephrolithiasis with flank pain and hematuria	Supportive care; renal dysfunction resolved in all cases
<i>Vaccinium macrocarpon</i> (Cranberry; n = 1) [53]	Daily dose unknown; ingested for 6 months	Nephrolithiasis with flank pain and hematuria	Supportive care; renal dysfunction resolved
Rhabdomyolysis-induced nephrotoxicity			
<i>Artemisia absinthium</i> (Wormwood oil; n = 1) [54]	10 ml × 1 dose	Tonic-clonic seizures resulting in AKI	Supportive care; renal dysfunction resolved
Creatine monohydrate (n = 5) [55–57]	5–25 g/day; duration unknown	Extreme muscle pain after participating in strenuous exercise; compartment syndrome (4/5) and AKI	HD, supportive care; one patient died of multisystem organ failure in all other cases renal dysfunction resolved

Table 1. (continued)

Natural product (n)	Dose	Renal manifestations	Management/outcomes
<i>Glycyrrhiza glabra</i> (Licorice; n = 2) [58, 59]	Daily doses of up to 280 mg/day; duration of 4 months and 7 years	Nephrotoxicity secondary to hypokalemia, severely damaged tubular cells with intense vacuolar formations	Supportive care; renal dysfunction resolved
Caffeine with taurine (n = 1) [60]	780 mg/day of caffeine and 4,600 mg/day of taurine; duration unknown	AKI	HD and supportive care; renal dysfunction resolved
Hepatorenal syndrome			
<i>Hedeoma pulegioides</i> (Pennycroyal; n = 3) [61–63]	Daily dose and duration unknown	Edematous and hemorrhagic kidneys with ATN	Supportive care; all patients died secondary to these events
Hydrazine sulfate (n = 1) [64]	180 mg/day, ingested over 4 months	Progressive renal failure with autolysis of the kidneys	HD and supportive care; unknown outcome
<i>Thevetia peruviana</i> (Yellow oleander; n = 4) [65]	Daily dose and duration unknown	AKI; 1 patient with autopsy findings showing renal tubular necrosis with vacuolar formations	HD and supportive care; 3 patients died and in one, renal dysfunction resolved

AIN = Acute interstitial nephritis; ATN = acute tubular necrosis; CKD = chronic kidney disease; HD = hemodialysis; PP = plasmapheresis.

Table 2. Adulteration/contamination of natural products and their related nephrotoxicity [13]

Heavy metals	Renal toxicity
Mercury	Damage to the renal proximal tubule and heme-biosynthetic pathways
Lead	Chronic interstitial nephritis
Arsenic	Renal tubular necrosis; tubular degeneration; lymphomonocytic infiltration

mon. Many natural products are contaminated with heavy metals during the process of growth and cultivation [1]. Heavy metals have the potential to cause significant renal damage through various mechanisms (table 2) [13].

One of the most infamous adulterants leading to renal dysfunction was seen in cases of ‘Chinese Herb Nephropathy’ [14]. Case reports of healthy women who ingested the same weight-loss supplement and developed rapidly progressing renal failure exist. Chromatographic analysis of the supplement revealed that the natural product had been adulterated with *Aristolochia*, which contains aristolochic acid. The major renal injury was interstitial fibrosis with tubular atrophy and loss [14]. An increase in urothelial malignancies has also been observed in patients with cumulative exposure to aristolochic acid of more than 200 g [15]. In a case of 31 posttransplant and 8 hemodialysis patients exposed to aristolochic acid that developed renal failure and underwent prophylactic removal of the

nonfunctioning kidneys and ureter, biopsies of the kidney samples revealed urothelial carcinoma in 46% of the 39 patients. Urothelial lesions were also present in 44% of patients as a result of mild to moderate dysplasia [15].

Conclusion

It is known that individuals with or at risk of renal dysfunction may be particularly vulnerable to the harmful effects of natural products, either through renal complications associated with some natural products, or as a result of accumulation of the natural product secondary to reduced renal clearance. Grubbs et al. [16] described the use of natural products that were potentially harmful in persons with and at risk of renal dysfunction in a nationally representative sample. This analysis revealed that approximately 1 in 12 US adults is taking at least one natural product that is potentially harmful in persons with kidney disease. They also noted that even a pre-existing diagnosis of chronic kidney disease did not reduce the likelihood of taking a natural product with these harmful effects [16].

Natural products are generally viewed as safe and effective alternatives to prescription and/or nonprescription medications. The lack of standardized policies and regulations complicates the use of natural products. However, it is imperative that patients comprehend the potential dangers associated with consuming natural products, especially when done without consultation with a healthcare professional.

The potential for damage to the kidneys from natural products is a real concern. However, readers must understand that most of the evidence discussed here were from case reports, which do not prove a definitive cause-and-effect relationship. In addition, information on dosing and duration was often missing or secondary to patient recall, which complicates the identification of tolerated versus toxic doses. The present data are not fully conclusive, but does warrant caution and close monitoring, especially in patients at a higher risk for renal dysfunction. It is essential that both patients and healthcare providers play an active role in identifying natural product use and

in avoiding anticipated complications. Open communication with patients and sufficient education regarding natural products is warranted.

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Disclosure Statement

The authors declare no conflicts of interest.

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