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Aristolochic Acid (Chinese-herb) Nephropathy

By HUONG THI BICH TRAN, MD, and LI-LI HSIAO, MD

In recent years, Chinese herbs have gained popularity as alternative health supplements in the Western world. Nearly 80% of the world's population use traditional medicine for primary health care (World Health Organization [WHO], 1985). In 2000, the Australian population spent \$2.3 billion (AUD) on complementary and alternative medical (CAM) treatments, nearly 4 times the public payments for all pharmaceuticals.¹ In the United States (US), the use of herbal and dietary supplements has grown faster than any other CAM treatments. A recent survey revealed that 42% of the US population use alternative therapies, with herbal supplements comprising 12% of these supplements, at a cost of \$5 billion annually.² Chinese herbal remedies have also been prescribed in over 3,000 clinics in the United Kingdom (UK),³ and two-thirds of the Hong Kong population choose Chinese herbal medicine as an alternative or complementary source of health care.⁴ It is clear that the use of Chinese herbal medicines will be expected to grow. This issue of *Nephrology Rounds* examines the reports of renal failure with the use of herbal remedies; it reviews the background, metabolism, pathophysiology, and nephropathy of aristolochic acid-containing herbs in CAM.

Background

In 1992, 2 cases were reported in Belgium of women who presented with extensive interstitial fibrosis and severe tubular loss without glomerular lesions. Both patients rapidly progressed to end-stage renal disease (ESRD) and renal failure.⁵ Pertinent medical history revealed that both women had attended the same weight-loss program, which included the use of a regimen containing Chinese herbs. In 1993, an epidemiological survey was conducted at 6 dialysis units in Brussels, Belgium, and 46 additional cases were identified as herbal medicine-induced renal failure.⁵ Later, there was an outbreak of rapidly progressive renal fibrosis in Belgium involving at least 100 patients; most were middle-aged women taking a weight-loss regimen that included a mixture of Chinese herbs.^{4,6}

Many hypothesized that these herbs were responsible for the development of renal failure. Tetrandrine, the alkaloid of *S tetrandra*, was not found in the regimen. Instead *Aristolochia fangchi*, an aristolochic acid (AA)-containing herb was identified in 10 of 12 batches that claimed to contain *S tetrandra*. The substitution occurred due to the confusion between 2 Chinese herbs: *A fangji* and *A fangchi*. The former is *S tetrandra*, which does not contain AA, whereas the latter does. A similar confusion also occurred between *ChuanMuTong* and *GuanMuTong*. The former, *Clematis montana*, contains no AA, while the latter, *A manshuriensis*, does.

Serotonin agonists and sympathomimetic agents are known renal vasoconstrictors that may cause ischemia resulting in renal failure with interstitial fibrosis. Mengs et al⁷ reported that Wistar rats fed AA alone developed renal failure with rapid tubular necrosis. Many cases of AA-induced renal failure reported in Japan, Belgium, Spain, France, and the UK had no presence of serotonin agonists. As a result, AA was found to be the main causative nephrotoxic agent. The disorders with this clinical presentation are named Chinese-herb nephropathy (CHN) or AA nephropathy (AAN).

The actual number of patients exposed to AA in Belgium was unknown. Approximately 1,500–2,000 people were thought to be exposed. About 3%–5% of this population is affected with AAN. The small incidence of AAN may be due to:

- dose variation due to inconsistency among different batches
- patient compliance
- individual susceptibility to toxic and/or carcinogenic substances⁸
- endogenous metabolic variation.⁹

The AA-induced ESRD appears to be dose dependent; Martinez et al¹⁰ reported that the incidence rose from 30.8% to 77.8% when the cumulative AA dose increased from 0.99 g to 300 g.

Table 1: Reported cases of AAN outside of Belgium					
Author and year of publication	Reported countries	Clinical presentations	Type of herbs used	Reason of herb use	Duration of herb use
Pena, 1996 ¹²	Spain	50-year-old male with progressive renal failure	<i>Aristolochia pistolochia</i>	Nonspecific abdominal pain	4 years
Lord, 1999 ³	United Kingdom	49-year-old female with headache, hypertension; 58-year-old female with ESRD	Chinese herb mixture containing AAI and AAI	Eczema	2 years 6 years
Ubara, 1999 ¹³	Japan	61-year-old male with thirst and renal failure	Chinese herb mixture containing AA	Health supplements	7 years
Meyer, 2000 ⁴	United States	45-year-old female with ESRD	Chinese herb mixture containing AA	Pain relief	1 year
Tanaka, 2001 ¹⁴	Japan	5 patients (2 males, 3 females) with Fanconi's syndrome	Tenshin-toki-shigyaku-ka-gosyuy-syokyo-to	Cold extremities and atopic dermatitis	21 months–5 years
Yang, 2002 ¹⁵	Taiwan	60-year-old male with muscular weakness, severe hypokalemia and Fanconi's syndrome	Chinese herb mixture containing AAI and AAI	Kidney protection	5 months
Cronin, 2002 ¹⁶	United Kingdom	59-year-old male with renal failure and bone marrow suppression	Chinese herb mixture containing AAI and AAI	Treatment of hepatitis B	5 years
Lee, 2004 ¹⁷	Korea	43-year-old female with Fanconi's syndrome	Chinese herb mixture containing AAI and AAI	Weight loss	3 months
Arlt, 2004 ¹⁸	France	2 females, both 34 years old, with ESRD	Preparation number 28 containing AA	Weight loss	1.5, 9 months
Lo, 2005 ¹⁹	United Kingdom	60-year-old male with progressive interstitial nephritis, and bladder transitional cell carcinoma	<i>Aristolochia mollisemae</i> with AAI	Relapse of Crohn's disease	2 months
Hong, 2006 ¹¹	Taiwan	10-year-old male with Fanconi's syndrome and progressive renal failure	Chinese herb mixture containing AAI and AAI	Health supplements	3 years
Laing, 2006 ²⁰	United Kingdom	30-year-old male with renal failure and transitional cell carcinoma of bladder	Longalan Xieganwan (contains <i>Aristolochia manshuriensis</i>)	Enhancing liver function	5 years

AAN = aristolochic acid nephropathy; ESRD = end-stage renal disease

Since the early reports of herbal medicine-induced renal failure in Belgium, hundreds of additional cases have been reported in Japan, Taiwan, China, Hong Kong, the UK, Spain, France, and the US.⁹ In these reports, patient age ranged from 10 to 61 years, and the majority of patients were female.¹¹ The purposes for using the herbal products included weight control, health supplements, chronic eczema, pain relief, and hepatitis. In addition to *A fangji*, the use of other *Aristolochia* species such as *A pistolochia*, *A mollissima*, and *A manshuriensis* were also reported; they were used either alone or mixed with other herbs. Regardless, all these herbal products were found to contain AAI and AAI, the 2 major derivatives of AA. The onset of AAN leading to rapidly progressive ESRD ranged from 2 months to 7 years. Most patients had a typical clinical presentation similar to patients with AAN in Belgium; however, some patients presented with Fanconi's syndrome or hematuria due to transitional cell carcinoma of the bladder (Table 1).^{3,4,11-20}

Aristolochic acid: structure and metabolism

Aristolochic acid is found in *Aristolochia* and *Asarum* species; both belong to the Aristolochiaceae family. AA can be identified in several *Aristolochia* species such as *A contorta*, *A debilis*, *A fangji*, and *A manshuriensis*.

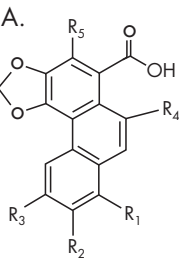
AA is a compound, structurally related to nitrophenanthrene carboxylic acid and its derivatives (Figure 1A); there are 11 derivatives of AA, namely AAI, AAI, AAI, 7-OH-AAI, AAI, AAI, AAVIIa, AAC, AAD, aristolic acid, and

aristofolin B. AAI and AAI, which differ from each other by only 1 methoxyl group (Figure 1B), are the major ingredients of AA, while the other derivatives are present only in minor quantities.

Observations from *in vitro* studies using the LLC-PK1 cell line, porcine proximal tubular epithelial cells, demonstrated that AAI had cytotoxic effects. Among all the AA derivatives, AAVIIa and AAIa also have cytotoxic effects, but of lesser intensity.¹² The “nitro” group (-NO₂-) in the R4 position and the “methoxyl” (-OCH₃-) group in the R1 position are critical in determining maximum toxicity. Any modification of the AAI structure drastically reduces its cytotoxic effect. This is supported by reports that AAI loses its cytotoxic effect during the process of nitroreduction. AAI, which has the methoxyl group removed from the R1 position, has reduced cytotoxicity.²¹

The mechanisms of AA metabolism are unclear thus far. Krumbiegel et al²² reported that when rats received orally administered AAI or AAI, AAI became AAIa via demethylation and, subsequently became aristolactam-Ia (ALIIa), a stable metabolic end product. The majority of these processes occurred under aerobic conditions, and minimal processes occurred under anaerobic conditions. In contrast, there is no metabolic activity for AAI under aerobic conditions;⁸ 46% of the ALIIa is excreted in urine and 37% in feces. For ALII, the major metabolite of AAI, 4.6% is excreted in urine and 8.9% in feces. Similar observations were also made in mice; however, no metabolites are found in the urine of guinea pigs, rabbits, dogs, and humans.²²

Figure 1: Structure details of nitrophenanthrene carboxylic compounds

A.		B.	Name	R1	R2	R3	R4	R5
	AA I	OCH ₃	H	H	NO ₂	H		
	AA II	H	H	H	NO ₂	H		
	AA III	H	H	OCH ₃	NO ₂	H		
	AA Ia	OH	H	H	NO ₂	H		
	7-OH AA I	OCH ₃	OH	H	NO ₂	H		
	AA VIa	OCH ₃	H	H	NO ₂	OH		
	AA VIIIa	OH	OCH ₃	H	NO ₂	H		
	AA C	H	H	OH	NO ₂	H		
	AA D	OCH ₃	H	OH	NO ₂	H		
	Aristolochic acid	OCH ₃	H	H	H	H		
	Aristofolin B	OCH ₃	OH	H	H	H		

Aristolactams (ALs), the principal metabolites of AAI and AAI, have 9 derivatives. While ALI and ALII have been reported to have carcinogenic and nephrotoxic effects,²³ these effects have not been associated with the other 7 AL derivatives.

The acute tubular damage caused by AA appears to be dose and species dependent. In rabbits, tubular damage can be induced by a single intravenous injection of 1 mg/kg. In humans, it required 1 mg/kg/day for 3 days in a phase I clinical study.²⁴ In rats and mice, single doses of 20 mg/kg and 30 mg/kg are needed, respectively.²⁵ There are no acute tubular lesions observed in dogs, cats, frogs, and porpoises after AA administration.⁸

Multiple methods have been used to detect AA, including ultraviolet (UV) spectrophotometry, thin-layer chromatography scanning (TLCS), high-performance liquid chromatography (HPLC), liquid chromatography electrospray mass spectrometry (LC/MS), and capillary zone electrophoresis (CZE). Reversed-phase high-performance liquid chromatography with diode array detection (RP-HPLC-DAD) is by far the most sensitive modality; it can detect 5 AAs (AAI, AAI, AAI, AAI, AAI), 9-hydroxy AAI, and 2 ALs (ALI and ALII) in 20 minutes.²³

Clinical presentation

AAN can develop as early as 2 months postexposure and up to 3 years after the discontinuation of treatment.^{4,5,8} The condition is more commonly seen in young females. Patients are typically asymptomatic, and the diagnosis is usually made through abnormal laboratory findings indicating renal insufficiency.

Patients with AAN commonly present with:

- anemia, out of proportion to the degree of renal failure
- mild proteinuria, consisting mostly of low-molecular weight proteins such as β 2-microglobulin, cystatin C, Clara cell protein (CC 16), retinol binding protein, which is found in increasing levels in urine, and neutral endopeptidase (NEP), an ectoenzyme of the proximal tubular brush border. Finding these proteins in the urine signifies damage of the proximal tubules.^{6,26} Furthermore, low-molecular weight proteinuria can be detected prior to any demonstrable decline in the glomerular filtration rate (GFR)^{27,28}
- normal to mildly elevated blood pressure
- glycosuria or leukocyturia in about 40% of urine samples
- significantly shortened serum creatinine doubling time
- progression to ESRD is more rapid than in other tubulointerstitial nephropathies.

About two-thirds of affected individuals eventually require renal-replacement therapy. It is important to emphasize that renal failure can continue to progress despite discontinuation of exposure to the herb.⁶

Pathology

Patients with AAN present with extensive interstitial fibrosis and tubular atrophy.⁸ These morphological changes are seen in a unique fashion with a gradient of intensity ranging from most severe in the outer cortex to less severe in the inner cortex and medulla. Furthermore, there is remarkable interstitial hypocellularity with few lymphocytic infiltrates interspersed among tubular epithelial cells and, essentially, no granulocytes. Another characteristic feature of AAN is that the glomeruli are relatively spared compared with the extensive tubular fibrosis. The thickening of the interlobular and afferent arteriole walls is most likely the result of endothelial cell swelling; immunofluorescence studies are usually negative.^{4,8}

Balkan endemic nephropathy

Balkan endemic nephropathy (BEN) is a chronic renal interstitial fibrosis with a slow progression to ESRD and urothelial malignancy. BEN is an environmental disease that is found in certain areas of the Balkan region, along the Danube river basin (Bulgaria, Bosnia, Croatia, Romania, and Serbia). The disease was discovered over 50 years ago and has affected at least 25,000 individuals. Multiple causative agents are proposed, including:

- fungal mycotoxin ochratoxin A (OTA)
- polycyclic aromatic hydrocarbons (PAHs) and other toxic organic agents leaching into well drinking water
- AA from flour contaminated with seeds of *A. clematitis*.^{9,10,17}

With the evidence of AA and OTA in the urothelial cancer tissue of the farmers living in endemic areas for BEN, chronic low-dose AA combined with OTA toxicity are regarded as risk factors for BEN-associated urothelial cancer.¹⁷

Differential diagnosis

The association of interstitial fibrosis, urothelial atypia, and malignancy in AAN is similar to analgesic nephropathy (AN) and BEN (Table 2).^{8,29}

Aristolochic acid and the risk of AAN-associated cancer

Urothelial lesions associated with AAN are common; rats fed with 0.1 mg, 1.0 mg, and 10 mg AA/kg body weight/day for 3 months demonstrated a high incidence of tumors (25%, 85%, and 100%, respectively). The organs found to have a high association with AA-induced tumor formation included the forestomach (77%), kidney (28%), and urinary tract (17%). Cosyns et al³⁰ studied 19 kidneys and ureters removed from 10 patients with AAN during and/or after renal transplant. Almost all patients developed multifocal moderate atypia in the medullary collecting ducts, pelvis, and ureters, especially those who consumed >200 g total accumulative dose of *A. fangchi*; 40% developed multifocal high-grade flat transitional cell carcinoma *in situ* (CiS), primarily located in the upper urinary tract. Recurrent noninvasive papillary transitional cell carcinoma (TCC) of the bladder was also observed. All CiS, papillary TCC, and urothelial atypia were found to have overexpressed p53.³⁰ Deoxyribonucleic acid (DNA) adducts were seen in kidney

Table 2: Differential diagnosis of AAN, AN, and BEN			
	Aristolochic acid Nephropathy (AAN)	Analgesic nephropathy (AN)	Balkan Endemic Nephropathy (BEN)
Duration of medicine use	2 months to 3 years	Long-term use, usually for years	No history of herb or analgesic use
Characteristics	90% female History of AA-containing herb use	Female > male Patient with history of chronic pain and analgesic abuse	Female = male Familial and environmental cluster
Anemia	Develops early and severe	Develops early and severe	Develops early and severe
Hypertension	50%	40%-50%	40%
Urinalysis	Mild tubular proteinuria, microscopic hematuria	Microscopic hematuria	Mild tubular proteinuria
Pathology	Acellular or hypocellular interstitial fibrosis, tubular atrophy, focal mononuclear cellular infiltration, normal or globally sclerosed glomerula. No interlobular elastosis, no papillary necrosis	Diffuse renal papillary necrosis	Similar to AAN, except interlobular fibroelastosis found in 35% of preuremic BEN kidney samples
Renal ultrasound	Bilateral renal homogenous atrophy with smooth outline and no calcifications	Bilateral renal atrophy with bumpy contours and papillary calcifications	Similar to AAN
Length of time toward ESRD	6-24 months		>20 years
Risk of upper urinary tract malignancy	50%-60%, discovered malignancy from 2-6 years after exposure	5%-24% 3.7%-14.1 after kidney transplant	40%, discovered after long exposure time (20-27 years).
Gene related to carcinogenesis	p53 mutation ³⁰	p53 mutation	3q25 and 3q26 mutation ²⁹

tissue lasting an average of 73 months after discontinuation of AA use.¹⁷

The most abundant DNA adduct detected by ³²P-postlabeling in urothelial tissue is dA-AAI. Evidence indicated that dA-AAI remained in various organs of AA-fed rats for a prolonged period of time. In fact, dA-AAI can be detected in patients with AAN 10 years after the use of herbs ended.³¹ These observations suggest that AA-induced DNA adducts can serve as a biomarker for AA exposure and cancer risk.

In December 2002, the International Agency for Research on Cancer (IARC) classified herbal remedies containing *Aristolochia* species as human carcinogens (Group 1); it also classified naturally occurring mixtures of AAs as probable human carcinogens (Group 2A).³²

Due to the strong association of urothelial cell atypia, CiS, and TCC, in kidneys with AA exposure from patients with AAN, Cosyns et al³⁰ recommended complete removal of native kidneys and ureters during or after renal transplantation, followed by frequent urinary cytological evaluation and surveillance cystoscopy. They also recommended that these patients be screened for bladder cancer every 3 to 6 months.

Pathophysiology

The pathophysiology of AA-induced nephrotoxicity is unclear. The salt-depleted Wistar rat was used to study AA-induced renal fibrosis. Debelle et al³³ found that only high-dose AA (20 mg/kg body weight) exposure could cause tubular dysfunction, tubular necrosis, and atrophy with lymphocytic infiltration on Day 10. On Day 35, these structural changes were surrounded by interstitial

fibrosis. However, urothelial dysplasia was observed in both high-dose (20 mg/kg) and low-dose (10 mg/kg) AA-treated groups and fibrohistiocytic sarcoma at the site of injection was observed in both groups.³³

Lebeau et al,³⁴ using the AAN model in Wistar rats, detected structural and functional proximal tubular impairments in the first 3 to 5 days of treatment. AA-related DNA adducts could be detected as early as Day 1 and were persistently present up to Day 35. In this experimental model, the dose of AA required to induce AAN was 30 times higher than that for CHN patients (1 mg/kg). Furthermore, renal function of the animals recovered by Day 14 after withdrawal of AA with signs of tubular regeneration. This was different from clinical presentations observed in humans.

The opossum kidney (OK) cell line, a proximal tubule epithelial cell line, was treated with AA for 24 hours *in vitro*.³⁴ AA was found to inhibit endocytosis activity, a step involved in protein reabsorption. The inhibition resulted from a decrease in the number of recycling receptors; this process was irreversible even after the termination of AA treatment. These findings suggest that AA-induced toxic effects may be related to the sustained reduction of protein(s) involved in receptor-mediated endocytosis. This was supported by an observation that AA-treated cells had decreased megalin expression, which is a receptor for endocytosis of low-molecular weight proteins.³⁴ Using the Madin-Darb canine kidney cells, Hsin et al³⁵ demonstrated that AA evokes a rapid rise in intracellular calcium concentration in renal tubular cells by releasing the intracellular endoplasmic reticulum calcium stores and an influx of extracellular calcium. This causes stress on

the endoplasmic reticulum and mitochondria that subsequently results in activation of caspase and, finally, apoptosis.³⁵

High-dose AA is known to cause acute tubular necrosis, but currently there is no experimental model to demonstrate chronic effects of AA nephrotoxicity. Cosyns et al³⁶ found that rats fed AA for prolonged periods failed to develop any chronic renal lesions, despite the development of malignancies in their digestive systems and urinary tracts. In another study, Cosyns et al³⁷ administered AA to female New Zealand white rabbits via the intraperitoneal space, at a concentration of 0.1 mg/kg/day (6 times higher than the dose in AAN/CHN patients). The compound was given 5 days/week for 17–21 months (a longer exposure time than in humans), and the reported results revealed interstitial fibrosis with hypocellularity and tubular atrophy.

Questions have been raised about the contributions of other compounds found in the slimming regimens leading to the development of AAN. Dexfenfluramine (DXF; 7 mg/kg), an appetite suppressant and strong vasoconstrictor, was studied in combination with AA (7 mg/kg) in salt-depleted Wistar rats. The combination of these 2 compounds caused rapid weight loss after 4 days of treatment, versus 14 days in animals treated with AA alone. The rats treated with a combination of DXF and AA did not show an enhancement of the tubular necrosis, lymphocytic infiltration, or interstitial fibrosis when compared with AA-alone treatment, after administering the regimens subcutaneously daily for 35 days. However, a significant increase in AA-DNA adduct levels in kidney tissues was observed in the DXF + AA treatment group as compared to those treated with AA alone.³⁸

The mechanisms of AA-induced interstitial fibrosis are not yet clear. The rapid progression of chronic tubulointerstitial renal disease may have been caused by the use of a potent nephrotoxic substance, such as AA on a background of fenfluramine/diethylpropion-related sustained renal vasoconstriction.²⁹ The possibility of AA-induced transdifferentiation of renal tubular epithelial cells into a myofibroblastic phenotype is currently under investigation. Recently, rats treated with AA (10 mg/kg, 5 times/week for 3 months) were used as an animal model for a toxicogenomic study to examine the consistency of microarray platforms.³⁹ To examine the AA-induced genetic effects on the kidney, Hsiao et al identified 47 genes that are differentially expressed between AA-treated and control rats (data not shown). Further studies are needed to advance the understanding of the functional mechanisms in AA-induced nephrotoxicity.

Treatment

Currently, there is no proven treatment for AAN. One study suggested that corticosteroids, at a dose of 1 mg/kg/day for a month and then tapered, might slow the rate of progressive renal failure.⁴⁰ However, studies also indicated that steroids may not be efficacious due to the absence of interstitial infiltrate.⁴⁰ The use of renoprotective agents such as angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor

blockers (ARB) may not be beneficial.⁴ The lack of response to inhibition of the renin-angiotensin system (RAS) in AAN may be due to:

- the rate of progression to ESRD being too rapid for RAS blockade to be effective⁴
- the renoprotective effects of the RAS blockade are largely attributed to its ability to reduce proteinuria, in particular, glomerular proteinuria. AA-induced proteinuria is a consequence of proximal tubular damage, rather than glomerular barrier alteration, which may explain the absence of benefits with RAS blockade.⁴¹

For individuals with AAN who have undergone renal transplant, there is no evidence that post-transplant immunosuppressants cause enhancement in the development of uroepithelial tumors or a recurrence of AAN.³⁰

Development of multifocal, recurrent papillary transitional cell carcinoma of the urothelium and bladder remains the most fearful complication of AAN/CHN, BEN, and analgesic abuse nephropathy; frequent vigilant screening for a lengthy period remains essential for patients at risk.

AAN and healthcare systems

Herb products containing AA are no longer allowed commercially in several countries, including the US. However, AA-containing products can still reach individuals readily and easily. In particular, it is recognized that language barriers prevent both customers and practitioners from effectively verifying the ingredients listed on many Chinese herbal products. This is especially challenging when the herbs are sent as gifts from one country to another; it also proves to be particularly perplexing for control and monitoring by officials. Furthermore, the lack of surveillance enables individuals to purchase herbal products via the Internet with no valid prescriptions or expert advice from experienced herbalists. It is also difficult to validate the legitimacy of merchants as well as the quality of the products.⁴² The lack of government regulation on herbal supplements opens the market to a wide over-the-counter (OTC) array of natural herbal products. Finally, the crude preparation of herbal medicine, either in raw materials or in powder form, leave many opportunities for error and substitutions. The accidental dispensing of AA-containing herbs is further magnified because the compound is present in many botanical species.

The Chinese Medicine Research Group from Australia screened 27 commonly used Chinese herbs and 7 popular manufactured products. They found that 6 out of the 34 tested products contained AA ingredients. In fact, the confusion in Chinese nomenclature for related raw herbs and the imprecise labeling of manufactured products may contribute to the inadvertent use of toxic herbal species in the practice of Chinese medicine.⁴³

Conclusion

Since the first report of AAN in Belgium, several countries, including Canada, Australia, Germany,

the UK, and the US, banned the use of herbs containing AA. Although most Chinese herbs are probably safe, they may cause severe adverse effects when used without the supervision of experienced herbalists. In view of the serious consequences that may arise, the source of products and the production and dispensing of naturopathic and homeopathic medicines should be regulated by the Food and Drug Administration (FDA) to avoid any potential hazards. In addition, the FDA should require dosing and efficacy testing on all herbal products, and the same truth-in-marketing laws required for all other medicines should be applied to herbal products. Finally, it is of critical importance that physicians and the general population be educated about AA-induced nephrotoxicity, carcinogenicity, and mutagenicity.

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