Special Report

Herbs and Hazards

Risk of Aristolochic Acid Nephropathy in Iran

Mohammad Reza Ardalan,[1] Laleh Khodaie,[2] Hamid Nasri,[3] Abolghasem Jouyban[4]

[1]Chronic Kidney Disease Research Center, Tabriz University of Medical Sciences, Tabriz, Iran
[2]Department of Traditional Pharmacy, Faculty of Traditional Medicine, Tabriz University of Medical Sciences, Tabriz, Iran
[3]Department of Nephrology, Division of Nephropathology, Isfahan University of Medical Sciences, Isfahan, Iran
[4]Pharmaceuticalal Analysis Laboratory, Drug Applied Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

Keywords. medicinal plants, interstitial nephritis, Balkan Nephropathy, chronic kidney disease

Herbs are usually considered as inherently harmless products. Nonetheless, various renal injuries have been reported in association with several herbs. The best-known herb-induced chronic kidney disease is aristolochic acid nephropathy. Aristolochic acid is found in Chinese slim herbs. Balkan endemic nephropathy is nowadays considered as an aristolochic acid nephropathy. Plants of *Aristolochiaceae* (also known as *birthwort*, *dutchman's pipe*, and *somersworth*) is named *zaravand* or *chopoghak* in Persian and it grows in different mountainous and rural areas of Iran. The fruit and the steam of the *Aristolochiacae* are named *zaravand gerd* (*nokhod alvand*) and *zaravand dearaz*, respectively, and have different usage in Iranian teadirional such as treatment of headache, back pain, and anxiety. Some patients with end-stage renal disease and bilateral small kidneys have a history of exposure to some herbal remedies. We need to consider the possibility of environmental toxins and even *Aristolochia* nephrotoxicity as a potential danger in Iran.

IJKD 2015;9:14-7
www.ijkd.org

INTRODUCTION

Herbal therapy is usually considered as inherently harmless. Nonetheless, various renal injuries have been reported in association with several herbs. Tubular necrosis, acute interstitial nephritis, Fanconi syndrome, hypokalemia or hyperkalemia, hypertension, papillary necrosis, chronic interstitial nephritis, nephrolithiasis, and urinary retention all have been reported in association with herbal products.[1] Taiwan has the highest incidence of chronic kidney disease (CKD) and also has the highest rate of herbal medicine use.[2] There are also a tendency among CKD patients to adhere to this type of medicine.[1] Herbal remedies often are prepared by herbalists with no training, not tested for the content, and can be adulterated or contaminated with toxic chemicals, heavy metals, and pesticides. Confusing terminology, errors in identification, and substitution with a toxic substance all could happen and make it difficult to trace the exposure to a specific herb.[3-5]

The best-known herb-induced CKD is aristolochic acid nephropathy (AAN). The toxicity of the family of *Aristolochiaceae* has been known in different aspects. In goats, intoxication with *Aristolochia bracteatu* presents with loss of hair, increase in aspartate aminotransferase, ammonia and urea, and hemorrhage in the lungs, heart, and kidneys.[6,7] The condition first came under notice in humans when an unusual increased number of patients with interstitial nephritis were reported in Belgium, for which aristolochic acid in Chinese slim herb was found to be responsible. The condition was therefore named "Chinese herb nephropathy.[8]" This nomination should not denigrate the system of Chinese herbal medicine as many useful compounds has entered modern medicine from Chinese medicine.[9] Aristolochic acid nephropathy is characterized by small kidneys, tubular proteinuria, extensive interstitial fibrosis, and tubular atrophy. Urothelial malignancy sometimes develops in some of these patients.[10] Aristolochic acid-induced

Fanconi syndrome and acute kidney failure have also been reported.[4,11,12]

Balkan endemic nephropathy was first recognized in the 1950s along the Danube River and its tributaries in the Balkans, stretching into Romania, Bulgaria, Croatia, Serbia, and Bosnia Herzegovina. Aristolochic acid hypothesis in Balkan endemic nephropathy was initially proposed by Ivic in 1970; he suggested a possible chronic dietary intoxication by wheat flour contaminated with seeds of Aristolochia clematidis.[13]

ARISTOLOCHIA GENUS IN IRAN

Plants of *Aristolochiaceae* (*birthwort*, *dutchman's pipe*; also known as *zaravand* and *chopoghak* in Persian), grows in mountainous areas and agricultural fields. In Iran, they are distributed in Mazandaran, Azerbaijan, Kurdistan, Kermanshah, Ilam, Lorestan, Isfahan, Khuzestan, and Tehran provinces. Perennial shrub of this genus grows to a height of 10 cm to 60 cm. It has reniform leaves and yellowish green flowers. The fruit is a globoid. Three herbaceous of *Aristolochia* are endemic to Iran. These include *Aristolochia bottae* Jaub & Spach (*Aristolochia Maurorum*), which is known as *zaravand*, *chopoghak*, *kalaghak* in Persian (Figure 1); *Aristolochia hyrcana* Davis (*Aristolochia iberica* Fisch & Mey), which is known as *chopoghak-e-rudbari* or *khazari* in Persian (Figure 2); and *Aristolochia olivieri* Collengo (*Aristolochia bruguieri* Jau & Spach), which is known as *chopoghak-e-zaghrosi* in Persian and also wild eggplant in Khorasan province (Figure 3). *Aristolochia bracteata* (*kharbuzeh abujahl*) have also been detected in the Alborz mountains.[14,15]

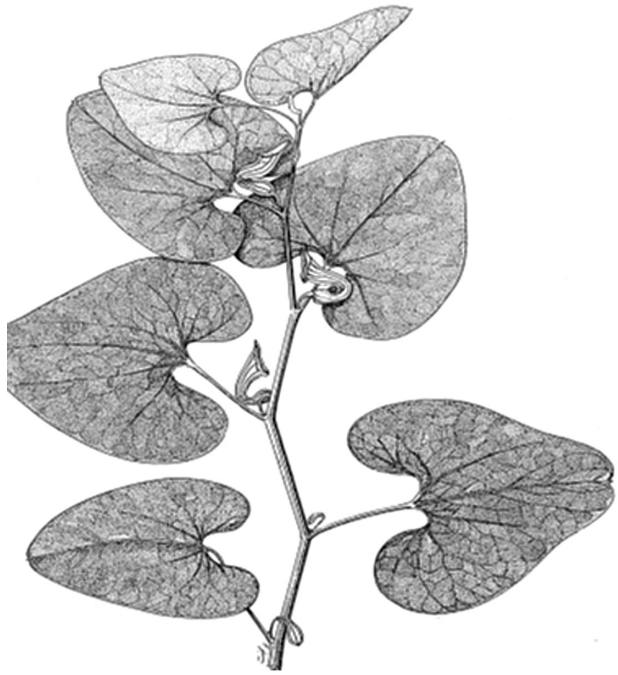

Figure 2. *Aristolochia hyrcana* Davis (Persian name: *zaravand*, *chopoghak-e-Rudbari*, or *Khazari*). Adapted with permission.[16]

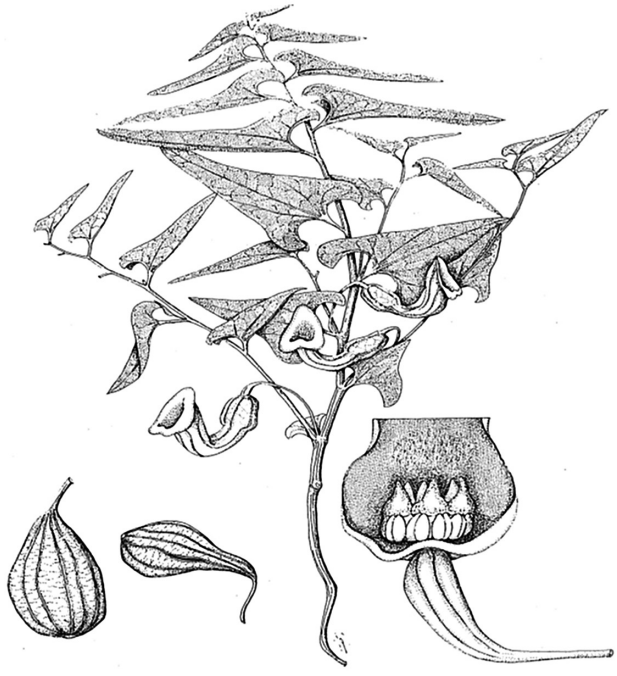

Figure 1. *Aristolochia bottae* (Persian name: *chopoghak* or *zaravand*). Adapted with permission.[16]

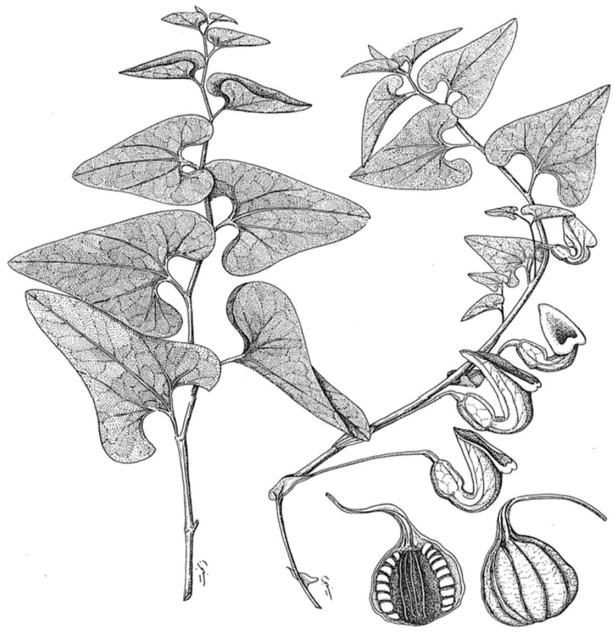

Figure 3. *Aristolochia olivieri* Collengo (Persian name: *zaravand*, *chopoghak-e-zaghrosi*). Adapted with permission.[16]

ARISTOLOCHIA IN IRANANIAN TRADITIONAL MEDICINE

Medicinal use of species of *Aristolochia* has been mentioned by the Greek scholar Dioscorides. It is an important medicinal plant in Indian-Ayurvedaic and Iranian traditional medicine. Its roots had been recommended as lithotripter, diuretic, menstruator, anthelmintic, expectorant, and carminative. It has been recommended for scorpion and insect bites and induction of abortion. *The steam of Aristolochia longa vulgaris* is named *zaravand deraz* in Iranian traditional medicine.[16]

Herbal products have many useful effects but raising the public awareness about the potential danger of herbal products is an emergent task.[17,18] Nowadays, there is a great vigor to propagate the absolute usefulness of herbal medicine herbal products. Sellers often are unscrupulous mediator who are not aware about the potential toxicity of herbs.[19,20] We have visited some herbal shops in different cities of Iran including Tabriz, Tehran, Isfahan, and Mashhad, and observed that the shop keepers are familiar with zaravand, selling of *Aristolochia* fruit for about 200 g for US $ 1. It is often named *round zaravand* or *zaravand modahraj*, or *nohkod alvand* (Figures 4 and 5). In one instance the seller instructed us as follows: "Grind 2 or 3 or 4 of those beans each time and mix it with honey and repeat it twice daily. It is useful for headache, back pain, and anxiety, and generally it detoxify all of your body."

Figure 4. The fruit of *Aristolochia Bottae* or *Aristolochia olivieri* Collengo. Its vernacular name in Iranian traditional medicine is *zaravand gerd*, *zaravand modahraj* (rotunda), or most commonly, *nokhod alvand*. It is sold for different medicinal purposes, including treatment of headache, backache, and anxiety, as an anti-helment, for induction of abortion, and as a general detoxifier.

Figure 5. *Aristolochia Rotunda* (*nokhod alvand*) on the shelf in a herbal medicine shop, lower row, third from the right.

Patients with end-stage renal disease and bilateral small kidneys are not infrequent in our daily experience. Some of them have a history of exposure to some herbal remedies. We should look in a bigger picture and consider the possibility of environmental toxins and even *Aristolochia* nephrotoxicity as a potential danger in Iran.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Isnard Bagnis C, Deray G, Baumelou A, Le Quintrec M, Vanherweghem JL. Herbs and the kidney. Am J Kidney Dis. 2004;44:1-11.
2. Hsieh CF, Huang SL, Chen CL, et al. Increased risk of chronic kidney disease among users of non-prescribed Chinese herbal medicine in Taiwan. Prev Med. 2012;55:155-9.
3. Jha V. Herbal medicines and chronic kidney disease. Nephrology. 2010;15;Suppl 2:10-7.
4. Debelle FD, Vanherweghem JL, Nortier JL. Aristolochic acid nephropathy. Kidney Int. 2008:74;158-69.
5. Byard RW. A review of the potential forensic significance of traditional herbal medicines. J Forensic Sci. 2010;55:89-92.
6. Barakat SE, Wasfi IA, Adam SE. The toxicit of Aristolochia bracteata in goats. Vet Pathol. 1983;20:611-6.
7. El Dirdiri NI, Barakat SE, Adam SE. The combined toxicit y of Aristolochia bracteata and Cadaba rotundifolia to goats. Vet Hum Toxicol. 1987;29:133-13.
8. Vanherweghem JL, Depierreux M, Tielemans C, et al. Rapidly progressive interstitial renal fibrosis in young women: association with slimming regimen including Chinese herbs. Lancet. 1993;341:387-39.
9. Cosyns JP. When is "aristolochic acid nephropathy" more accurate than "Chinese herbs nephropathy"? Kidney Int. 2002;61:1178-81.

10. Cosyns JP. Aristolochic acid and 'Chinese herbs nephropathy': a review of the evidence to date. Drug Saf. 2003;26:33-48.
11. Lo SH, Mo KL, Wong KS, et al. Aristolochic acid nephropathy complicating a patient with focal segmental glomerulosclerosis. Nephrol Dial Transplant. 2004;19:1913-5.
12. Yang L, Li X, Wang H. Possible mechanisms explaining the tendency towards interstitial fibrosis in aristolochic acid-induced acute tubular necrosis. Nephrol Dial Transplant. 2007;22:445-56.
13. Ivic M. Etiology of endemic nephropathy. Lijec Vjesn. 1969;91:1273-81.
14. Shamsa M, Saedi H. [Toxic plants and its toxicology in animals]. 6th ed. Tehran: Tehran University Publication; 1996. p. 7-58. Persian.
15. Majid M. [Iran's flora: Aristolochiacea]. Isfahan: Jungle and Pastures Research Institute; 1999. Persian.
16. Ardalan MR. Khodadoust K. [Lexicon of Persian medical terms in olden medical pandects, extracted from 10th century AD medical pandects]. Tabriz: Shervin Medical Publication; 2012. Persian.
17. Ardalan MR, Ostadrahimi A, Kohsoltani Y, Shoja MM, Ghafari A, Akbari A. Garlic (Allium sativum) prevents radiocontrast nephropathy following coronary angiography. J Nephrol Renal Transplant. 2012;4:34-9.
18. Rafieian-Kopaei M, Baradaran A, Rafieian M. Plants antioxidants: from laboratory to clinic. J Nephropathol. 2013;2:152-3.
19. Ardalan MR, Rafieian-Kopaei M. Is the safety of herbal medicines for kidneys under question? J Nephropharmacol. 2013;2:5-6.
20. Ardalan MR. Tabriz nephro-educational courses: a global scientific vision with local vigilance. J Ren Inj Prev. 2014;3:7-8.

Correspondence to:
Mohammad Reza Ardalan, MD
Chronic Kidney Disease Research Center, Tabriz University of Medical Sciences, Tabriz, Iran
Fax: +98 41 3336 6579
E-mail: ardalan34@yahoo.com

Received February 2014
Revised June 2014
Accepted July 2014