

Aristolochic acid: What urologists should know

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To the Editor,

Aristolochic acid is one of major causes for upper tract urothelial carcinoma, especially in younger population. While it is mentioned as a cause in guidelines, little is actually known about the toxin by urologists. We are aiming in our letter to provide some direct and clear information to ourselves that would help us to know more about that toxin and how it can adversely affect our patients.

What is Aristolochic acid?

Aristolochic acid is an acid obtained from a plant that grows in several areas of the world. Its use was started in China as an herbal medicine that was used to treat many diseases, then was advanced to be used in many herbal medications sold over the shelf worldwide (1).

Why people use that herbal drug?

This herbal supplement was long used as a miracle supplement for weight loss. Other less common uses were arthritis and menstrual problems (1). In Balkan areas; that herb was mixed with wheat used for home baked bread.

Importance to urologists

Aristolochic acid were found to be significantly associated with interstitial nephritis, end stage renal disease. This is currently known as a major cause of Balkan nephropathy (2). This was also proved to be a carcinogenic causing upper urinary tract urothelial carcinoma (3). A recent study (2017) looked for the oncological outcomes of patients with upper tract urothelial carcinoma exposed to Aristolochic acid. This was found to be significantly associated with higher rate of local and contralateral upper tract recurrence, as well as higher rate for intravesical recurrence (4). A recent meta-analysis and systematic review (2021) confirmed the same findings of higher rate of intravesical and contralateral recurrence for patients exposed to Aristolochic acid, as well as worse overall and disease specific survival (5).

Authorities' action and obstacles

The toxic and carcinogenic effect of Aristolochic acid was raising concerns since 1999. *Food and drug administration* (FDA) released warning in 2001 about the use of that herbal supplement and started to recall products from the market containing the acid. This was followed in 2004 by a warning from health Canada regarding the use of the supplement with an alert to the Canadian border to prevent importing the drug in any form (6, 7).

Why Aristolochic acid is a concern 20 years following authorities' action?

The concerns for Aristolochic acid are still existent for three important reasons. First; unlike other known factors as smoking, studies did show that patients that stopped the use of Aristolochic acid for more than 5 years were still at the same risk and worse oncological outcomes for upper tract urothelial carcinoma, similar to patients with recent exposure. It seems that exposure produces a permanent genetic alteration that keeps risking the patients' cancer development despite of cessation of exposure (4). The second problem is the natural growth of the plant in many areas of the world. While the plant may be avoided because of the known risks, studies have confirmed that the toxins of the plant can spread through the soil and affect other vegetables and fruits that can become contaminated by the toxins. That soil contamination leaching into rivers raised some concerns about water contamination in endemic areas where just drinking water may be imposing a risk for Aristolochic acid exposure. Another natural risk is through butterflies that can act as an intermediate host for the herbal contamination (8, 9). *Chan et al.* could recently (2016) identify Aristolochic acid in corn, wheat grains and soil samples taken from Balkan areas (10). More recent studies confirmed the same findings as the root vegetables in Balkan areas were found to be extensively contaminated with Aristolochic acid (11, 12). The last risk is through

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Table 1.
Plants containing Aristolochic acid (From FDA 2020).

Plant name	Common/alternative name	Plant name	Common/alternative name
Aristolochia spp.	Aristolochia Guan Mu Tong Guang Mu Tong	Aristolochia maurorum L.	
Aristolochia acuminata Lam. Syn. Aristolochia tagala Champ.	Oval leaf Dutchman's pipe	ristolochia mollissima Hance	
Aristolochia argentina Griseb.		Aristolochia pistolochia L.	
Aristolochia baetica Linn. Syn. Aristolochia bracteolata Lam.		Aristolochia rigida Duch.	
Aristolochia bracteata Retz. Aristolochia chilensis Bridges in Lindl. Aristolochia cinnabarina C.Y. Cheng & J.L. Wu	Ukulwe	Aristolochia rotunda Linn.	
Aristolochia clematitidis L.	Birthwort	Aristolochia serpentaria L. Syn. Aristolochia serpentariavar. hastata (Nutt.) Duch.	Virginia snakeroot Serpentaria Virginia serpentary
Aristolochia contorta Bunge	Ma Dou Ling Tian Xian Teng	Aristolochia serpentaria L. Syn. Aristolochia serpentariavar. hastata (Nutt.) Duch.	Virginia snakeroot Serpentaria Virginia serpentary
Aristolochia cymbifera Mart. & Zucc.	Mil homens	Aristolochia watsoni Wooton & Standley or Aristolochia watsonii Wooton & Standley Syn. Aristolochia porphyrophylla Pfeifer	
Aristolochia debilis Siebold & Zucc. Syn. Aristolochia longa Thunb. Syn. Aristolochia recurvilabra Hance Syn. Aristolochia sinarum Lindl.	Ma Dou Ling Tian Xian Teng Qing Mu Xiang Sei-mokkou (Japanese) Birthwort Long birthwort	Aristolochia westlandii Hemsl. or Aristolochia westlandi Hemsl.	
Aristolochia elegans Mast. Syn. Aristolochia hassleriana Chodat		Aristolochia zollingeriana Miq. Syn. Aristolochia kankauensis Sasaki Syn. Aristolochia roxburghiana subsp. kankauensis (Sasaki) Kitam. Syn. Hocquartia kankauensis (Sasaki) Nakai ex Masam. Syn. Aristolochia tagala var. kankauensis (Sasaki) T. Yamaz.	
Aristolochia esperanzae Kuntze		Asarum canadense Linn. Syn. Asarum acuminatum (Ashe) E.P. Bicknell Syn. Asarum ambiguum (E.P. Bicknell) Daniels Syn. Asarum canadense var. ambiguum (E.P. Bicknell) Farw. Syn. Asarum canadense var. reflexum (E.P. Bicknell) B.L. Rob. Syn. Asarum furcatum Raf. Syn. Asarum medium Raf. Syn. Asarum parvifolium Raf. Syn. Asarum reflexum E.P. Bicknell Syn. Asarum rubrocinctum Peattie	Wild ginger Indian ginger Canada snakeroot False coltsfoot Colic root Heart snakeroot Vermont snakeroot Southern snakeroot
Aristolochia fangchi Y.C. Wu ex L.D. Chow & S.M. Hwang	Guang Fang Ji Fang Ji Mokuboi (Japanese) Kwangbanggi (Korean) Fang Chi Kou-boui (Japanese)	Asarum canadense Linn. Syn. Asarum acuminatum (Ashe) E.P. Bicknell Syn. Asarum ambiguum (E.P. Bicknell) Daniels Syn. Asarum canadense var. ambiguum (E.P. Bicknell) Farw. Syn. Asarum canadense var. reflexum (E.P. Bicknell) B.L. Rob. Syn. Asarum furcatum Raf. Syn. Asarum medium Raf. Syn. Asarum parvifolium Raf. Syn. Asarum reflexum E.P. Bicknell Syn. Asarum rubrocinctum Peattie	Wild ginger Indian ginger Canada snakeroot False coltsfoot Colic root Heart snakeroot Vermont snakeroot Southern snakeroot
Aristolochia fimbriata Cham.		Asarum himalaicum Hook. f. & Thomson ex Klotzsch or Asarum himalaycum Hook. f. & Thomson ex Klotzsch	Tanyou-saishin (Japanese)
Aristolochia indica L.	Indian birthwort	Asarum splendens (F. Maek.) C.Y. Cheng & C.S. Yang	Do-saishin (Japanese)
Aristolochia kaempferi Willd. Syn. Aristolochia chrysops (Stapf) E.H. Wilson ex Rehder Syn. Aristolochia feddei H. Lévl. Syn. Aristolochia heterophylla Hemsl. Syn. Aristolochia mollis Dunn Syn. Aristolochia setchuenensis Franch. Syn. Aristolochia shimadai Hayata Syn. Aristolochia tibetica Franch. Syn. Isotrema chrysops Stapf Syn. Isotrema heterophylla (Hemsl.) Stapf Syn. Isotrema lasiops Stapf	Yellowmouth Dutchman's pipe	Bragantia wallichii R.Br. <i>Specimen exists at New York Botanical Gardens.</i> <i>Tropicos does not list this species as a synonym for any Thotte species. Kew Gardens Herbarium does not recognize the genera Bragantia. Until additional information is obtained the name used is as cited in J. Nat. Products 45:657-666 (1982)</i>	
Aristolochia kwangsiensis Chun & F.C. How Syn. Aristolochia austrozechuanica C. B. Chien & C. Y. Cheng			
Aristolochia macrophylla Lam. Syn. Aristolochia siphon L'Hér.	Dutchman's pipe		
Aristolochia manshuriensis Kom. Syn. Hocquartia manshuriensis (Kom.) Nakai Syn. Isotrema manshuriensis (Kom.) H. Huber	Manchurian birthwort Manchurian Dutchman's pipe Guang Mu Tong Kan-Mokutsu (Japanese) Mokuboi (Japanese) Kwangbanggi (Korean)		

currently existing other herbal supplements widely used worldwide. While the intentional inclusion of Aristolochic acid is currently not allowed, contamination of the available herbal supplement with Aristolochic acid is a continuous risk. *Abdullah et al.* (2017) examined 573 different samples lacking Aristolochic acid as one of the ingredients. They could identify the substance in 206 samples (36%). This was a surprising fact that 1/3 of herbal supplements in market could be contaminated with Aristolochic acid (13).

What are the herbs that can possibly contain Aristolochic acid?

There were many plants reported in a monograph published in 2018 that can possibly contain Aristolochic acid. Most of these herbs have common names that are far away from the original toxin name including Dutchman's pipe, Virginia snakeroot, Canada snakeroot, wild ginger and Indian ginger (14). More recently, FDA updated its plant lists providing warning to the manufacturers and the public against the use of large numbers of herbs that can potentially harbour the toxin (15). Table 1 illustrate the plants having the toxin.

Are there ongoing ways for population protection against the toxin exposure?

Herbal medicine is being used worldwide as an alternative medicine that can augment the traditional medicine. The main issues are the large number of plants that can be harbouring the toxin together with possible language barriers and the use of English names to some herbs that can be completely different and not presenting the herb containing the toxin. There is no guaranteed current way to confirm the absence of toxin from available herbal medicine. In 2018; four DNA sequences were identified in a large study as possible target areas to detect the toxin out of eleven different plants. These DNA sequences were *bclL*, *matK*, *ITS2* and *trnH-psbA* (16). DNA barcoding is promising and ongoing way to detect most of the herbs that can be having the toxin, although it may still miss some uncommon herbs.

CONCLUSIONS

Aristolochic acid is a currently existing possible risk factor for the development of nephropathy and upper tract urothelial carcinoma. Its actual contribution to new cases diagnosed with upper tract urothelial carcinoma may be underestimated. Awareness programs to the public for possible herbal supplements contamination with Aristolochic acid as well as testing all herbal supplements for possible contamination should be implemented. DNA barcoding is able to identify most common herbs containing Aristolochic acid but may be still missing uncommon herbs.

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