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Etiology of Balkan Endemic Nephropathy: An Update on Aristolochic Acids Exposure Mechanisms

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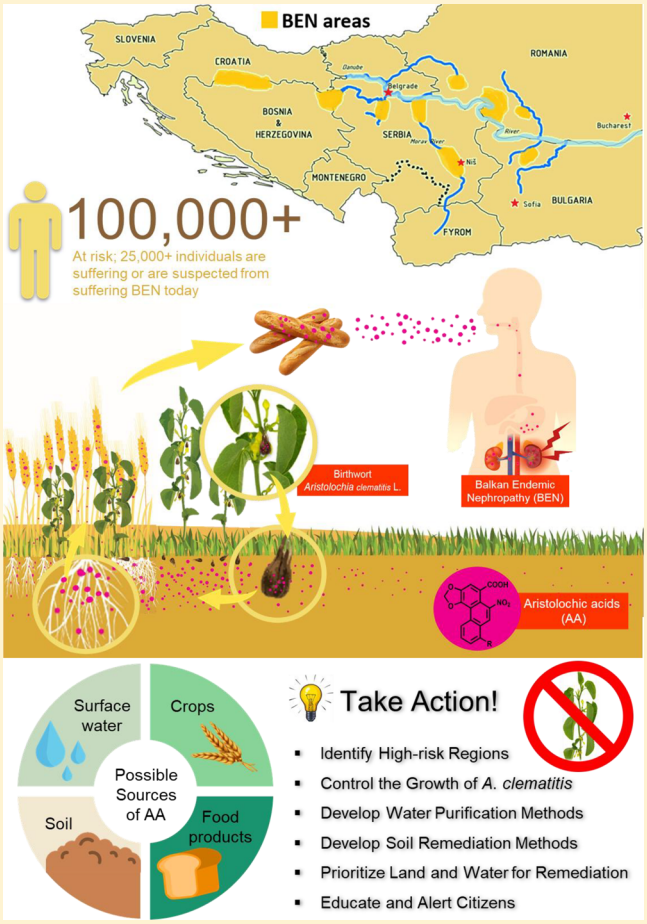
ABSTRACT: Aristolochic acid released from decaying *Aristolochia clematitis* weed is contaminating soil and food crops in Eastern Europe and is one of the major causes to Balkan endemic nephropathy. Measures should be taken to prevent people from being exposed to these highly potent phytotoxins. Research needs to develop remediation methods.



For over 60 years, residents of rural farming villages in Bosnia-Herzegovina, Bulgaria, Croatia, Romania, and Serbia have encountered a high prevalence of renal disease, known as the Balkan endemic nephropathy (BEN), a unique chronic kidney disease with slow and progressive loss of kidney functions.[1] Over 25 000 individuals are suffering, or are suspected of suffering, from BEN today, while the total population at risk is estimated to exceed 100 000.[2] Despite decades of intensive research into the etiology of BEN, which had explored genetic factor and various environmental contaminants including heavy metals, polycyclic aromatic hydrocarbons, or fungal toxins (especially Ochratoxin A) as potential causative agents,[2] a general consensus was not reached until more recently, when another class of phytotoxins, aristolochic acids (AAs), was shown to be the true culprit.

Since ancient times, *Aristolochia* plants and their extracts containing AAs have been adopted worldwide as herbal medicine for a wide range of symptoms and diseases such as arthritis, gout, and inflammation. With sufficient evidence substantiating AAs and their associated herbs' high nephrotoxicity and carcinogenicity to both laboratory rodents and human beings, they have been classified as Group 1 carcinogens (being carcinogenic to human) by the International Agency for Research on Cancer in 2002,[3] which has led to herbal

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medicines and botanical products that contain or may contain AAs being banned subsequently around the globe. Later, the U.S. Food and Drug Administration (FDA) advised consumers to stop using any botanical products that may contain AAs, and the European Agency for the Evaluation of Medicinal Products (current European Medicines Agency, EMA) also warned European Union member states "to take steps to ensure that the public is protected from exposure to AAs".

Aristolochia clematitis L. (or birthwort), an example of AA-containing plants, grows abundantly across many endemic fields in the Balkan Peninsula.[4] It was believed that the comingling of *A. clematitis* seeds with the wheat grains during annual harvesting has led to AA-contamination in food intended for human consumption.[1,4] The residents in the endemic regions consumed home-baked bread made from locally grown, AA-contaminated wheat flour as their dietary staple and thus would have been continually exposed to these highly potent nephrotoxins for prolonged periods.[1] This was first thought to be the etiology of BEN.

However, this proposed exposure pathway where AAs entered the human food chain via coharvesting of AA-containing seeds with wheat grain remained controversial. First, the seeds of *A. clematitis* and wheat mature at different times; while wheat is harvested in the early summer, *A. clematitis* weed would be flowering and barely beginning to produce green immature seeds, thus unlikely for the seeds of *A. clematitis* to become coharvested along with the wheat grains. Second, the typical size of an *A. clematitis* fruit (~30 × 40 mm^2) is significantly larger than that of a wheat grain (~3 × 6 mm^2). Significantly different sizes and weights would facilitate the removal of any seeds of *A. clematitis* during either the threshing or milling processes, even if they were coharvested with wheat grains. On top of that, the hypothesis failed to explain the endemic nature of the disease, as BEN incidence localizes in the rural regions of the Balkan countries, despite the fact that *Aristolochia* species are also native in many Asian, European, and North American countries.

The missing piece of the puzzle came through examining the soil in cultivation fields where wheat and maize grains were grown. The researchers discovered a previously unnoticed, health-threatening issue: as *Aristolochia* weeds decay, their AA contents are released and retained in the cultivation field soil. The free AAs are then taken up by neighboring food crops through their roots and subsequently deposited into the grains.[3] Data also indicated a facile positive correlation of food and soil contamination with the local incidence of BEN, which shed light on the geographical confinement of the disease. Results from this study have confirmed a new exposure pathway to AAs and helped toward painting the complete etiological picture of BEN.

Knowing that the nephropathy is localized in villages near tributaries of the Danube River, it is highly possible that the free AAs in soil would leach into wells and springs and be transported downstream into the River. Notably, the Danube is the drinking and irrigation water source for many locations; therefore, AA-pollution of the river water could threaten the safety for millions of people in the Balkan Peninsula. This translates to an urgent need for analytical methods that can detect AAs at trace levels in water samples.

Although both FDA and EMA have issued warnings and have advised consumers to minimize exposure to AAs, previous warnings merely focused on alerting individuals to avoid herbs or herbal supplements potentially containing AAs. Unfortunately, at the time of warning issuance, it was not yet known that AAs contamination has actually reached all the way into food grains and into the ambient environment, and thus, they made no specific mention of AAs-contaminated food and water. While any comingled seeds of *A. clematitis* weed could be removed from the wheat grains relatively easily during the milling process, AAs contents within wheat grains and drinking water would be much harder to eradicate. As a result, people in the affected areas are inadvertently and helplessly being exposed to these highly potent nephrotoxins.

With emerging evidence suggesting that AAs are persistent and widespread soil contaminants,[3,5] weed control for *A. clematitis* plants alone would not be sufficient to reduce the incidence of BEN and aristolochic acid nephropathy. Systematic surveys of AA levels in soil, surface water, food crops, and food products are necessary to identify high-risk regions. Furthermore, it is imperative to develop water purification methods, soil remediation methods, and to prioritize land and water for remediation. Last but not least, the local government must act in a timely manner to educate and inform their people about the existence of these totally unexpected toxicants in their food, drinking water, and the environment.

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Notes

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REFERENCES

(1) Grollman, A. P., Shibutani, S., Moriya, M., Miller, F., Wu, L., Moll, U., Suzuki, N., Fernandes, A., Rosenquist, T., Medverec, Z., Jakovina, K., Brdar, B., Slade, N., Turesky, R. J., Goodenough, A. K., Rieger, R., Vukelić, M., and Jelaković, B. (2007) Aristolochic acid and the etiology of endemic (Balkan) nephropathy. *Proc. Natl. Acad. Sci. U. S. A. 104*, 12129−12134.

(2) Tatu, C. A., Orem, W. H., Finkelman, R. B., and Feder, G. L. (1998) The etiology of Balkan endemic nephropathy: Still more questions than answers. *Environ. Health Perspect. 106*, 689−699.

(3) Chan, W., Pavlović, N. M., Li, W., Chan, C. K., Liu, J., Deng, K., Wang, Y., Milosavljević, B., and Kostić, E. N. (2016) Quantitation of aristolochic acids in corn, wheat grain, and soil samples collected in Serbia: identifying a novel exposure pathway in the etiology of Balkan endemic nephropathy. *J. Agric. Food Chem. 64*, 5928−5934.

(4) Ivić, M. (1969) Etiology of endemic nephropathy. *Liječ Vjesn 91*, 1278−1281.

(5) Li, W., Chan, C.-K., Liu, Y., Yao, J., Mitić, B., Kostić, E. N., Milosavljevic, B. S., Davinić, I., Orem, W. H., Tatu, C. A., Dedon, P. C., Pavlović, N. M., and Chan, W. (2018) Aristolochic acids as persistent soil pollutants: Determination of risk for human exposure and nephropathy from plant uptake. *J. Agric. Food Chem.*, DOI: 10.1021/acs.jafc.8b04770.

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