Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

International Journal of Surgery 108 (2022) 106992

Contents lists available at ScienceDirect

International Journal of Surgery

journal homepage: www.elsevier.com/locate/ijsu

Correspondence

Growing risk of aristolochic acid nephropathy in the era of COVID-19 – Correspondence

ARTICLE INFO

Keywords
COVID-19
Aristolochic acid
Nephropathy
COVID-19 vaccination

Dear Editor,

The ongoing coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARSCoV-2), has led to high mortality and a global pandemic for more than two years. SARS-CoV-2 severely affects persons who have other life-threatening diseases or puts them at a higher risk of contracting this infections disease. Aristolochic acids (AAs) are natural compounds found in many plant species belonging to the Aristolochiaceae family that can cause severe nephropathy and kidney cancer. The presence of AA in many herbal products on the global market would have widespread adverse effects on the disease patterns of AA-associated kidney cancer and nephropathy. The hazards of AA usage must be evaluated because the COVID-19 pandemic has not yet ended. In this correspondence article, we discuss AAs, their source, uses, as well as the link between COVID-19, aristolochic acid, and nephropathy. This article will help understand the effects of AAs in relation to COVID-19 and nephropathy.

Herbal supplements have grown in popularity over the last few decades. By 2027, it is expected that the market for herbal supplements will reach US$49.1 billion [1]. Since herbal supplements are made from natural sources, they are typically thought to be safe. Herbal supplements are not required to undergo premarketing purity or potency tests by the US Food and Drug Administration (FDA), unlike conventional pharmaceuticals. Direct ingestion of plants of the Aristolochiaceae family has been linked to renal damage and liver cancer, and because of the potent cancer-causing toxicity of Aristolochic acids (AAs), these have been in the news for a long time. Nonetheless, the current pandemic has pushed us to reconsider the impact of AAs in the context of COVID-19.

Nearly all Aristolochiaceae species, notably those belonging to the genera *Aristolochia* and *Asarum*, contain AAs, which are naturally occurring monocarboxylic acids with similar structural properties. These have mostly been used in Ayurvedic, Chinese, and other conventional folk medicine to reduce inflammations. For centuries, plant species from the genus *Aristolochia* have been used in South East Asia as a remedy for ailments such as pneumonia, malaria, diabetes, diarrhoea, and more [2]. This plant has been used since 400 AD, according to Chinese and Ayurvedic sources. *Aristolochia* was also recognised as a medicinal herb in ancient Greek and Roman medical writings [3]. However, AAs must be used with caution at the prescribed dose due to their nephrotoxic nature, and their extracts should be used with great care due to their cytotoxic and mitotoxic characteristics [11].

Aristolochic acid nephropathy (AAN) and renal fibrosis caused by AAs are known to increase the risk of upper urinary tract cancer. There are many mechanisms of AA-induced nephrotoxicity, including gene expression and epithelial cell reprogramming, apoptosis, and lower survival of renal cells due to ERK1/2-dependent and p38-dependent cell cycle arrest [12]. AAN was initially identified in a woman who had been using diet pills containing Aristolochia fangchi Wu ex Chow & S.M. Hwang in a clinic in Brussels, Belgium. Numerous nations around the world, including Germany, the United Kingdom, the United States of America, Australia, and Canada, have reported sporadic cases of AAN [15].

A person may consciously or unknowingly consume AAs through diet and during herbal remedies. In many nations, *Aristolochia* species-derived medicines and pharmaceuticals are widely used, and they are legal to buy online [2]. AAN poses a continual health risk to people who utilise traditional medicine and to urban consumers. The importance of AAN is that it serves as a reliable predictor of an increased risk for AA-related malignancies in the future [4,5]. However, no such direct link between AAN and COVID-19 has been discovered, although COVID-19 pandemics are linked to an increased risk of developing cancer, and COVID-19 infections are more common in persons who already have the disease.

Patients with cancer, notably those with kidney cancer, experience increased difficulties as a consequence of the COVID-19. The molecular link between COVID-19 and kidney cancer has already been discussed in several papers [16]. Epidemiological data to date suggests that people with cancer are more likely to get COVID-19. According to various studies from Wuhan, China, 2–4% of early COVID-19 cases developed chronic renal failure [13,14].

COVID-19 has posed a serious threat to human survival, especially for those with underlying medical conditions [6]. Rapid spread of SARS-CoV-2 and its devastating pandemic scenario prompted vaccines to be manufactured and administered around the world without screening their side effects. In spite of the fact that this was the need of the hour, recent evidence suggests that patients already suffering from a

https://doi.org/10.1016/j.ijsu.2022.106992
Received 13 September 2022; Accepted 6 November 2022
Available online 11 November 2022

variety of illnesses may experience adverse reactions to COVID-19 vaccines. One recent report documented IgA nephropathy (IgAN) following COVID-19 vaccination in a 73-year-old renal transplant recipient with a history of AAN. In 2021, a patient developed IgAN after receiving two doses of the adenovirus vaccine ChAdOx (AstraZeneca). In five weeks following the second dose, several symptoms appeared, including lower leg swelling, proteinuria, and elevated serum creatinine, along with 3–5 erythrocytes in urine sediment. In the following three weeks, proteinuria increased to 1.9 g/24 h and GF-CKD-EPI decreased to 35 ml/min/1.73 m^2, with erythrocytes in the urine sediment. The molecular mechanism underlying the regulation of immune-mediated glomerular diseases remains unknown, but proinflammatory cytokines have been shown to activate $CD4^+$ and $CD8^+$ T cells (Fig. 1). It might be possible that the adenovirus-based vaccine might induce off-target immune-mediated glomerular diseases. It is consistent with previous observations that immunocompromised solid organ recipients experienced inferior vaccination results [7]. The angiotensin-converting enzyme 2 (ACE2) binds to the spike protein of SARS-CoV-2 in intestines, kidneys, testes, gallbladders, and hearts. Chronic kidney disease (CKD) patients have been reported to have more severe COVID-19, but it has not been proven that this is due to an increase in the receptor. In mice with chronic kidney disease, AA was examined for its effect on renal and pulmonary ACE2, and renal function and ACE2 expression declined significantly. The Lung ACE2 expression was unaffected. Considering that ACE2 expression in the lungs to be unaltered [8], patients with CKD may not be at a higher risk of SARS–CoV-2 infection [8]. However, it is unknown how AA works to prevent renal ACE2 from being expressed.

The nephrotoxicity of AA has generally received more attention, especially in East Asia where the risk of untreatable exposure is greatest. It is controversial whether or not AA is used in many forms of Chinese medicine, and it is not advised to consume this biomolecule directly from the *Aristolochia* sp. The risk connected to AA use has already been mentioned in a number of papers. It is critical that the dangers of AA use are assessed because the COVID-19 pandemic is not yet over, and subsequent pandemics may certainly arise in future. The simple accessibility of this plant in China and India has led to the development of AA-mediated nephropathy in a number of individuals. As it is now known that COVID-19 vaccination might cause nephropathy in immunosuppressed patients with underlying AAN and most of the world population has received vaccination, it is important that patients under AA medication are continuously monitored, especially in India and China [9,10]. Governments must coordinate their efforts globally to limit the use of AAs or create a methodology for a prescribed dosage. This will help in the management of COVID-19 patients who may develop AAN as a result of AA use. Building community awareness of the risks of AA exposure is still a work in progress. This includes comprehending how widespread AA is in daily life and how it affects human health in its entirety.

Please state any sources of funding for your research

N/A.

Author contribution

Tuyelee Das-conceptualization, writing first draft, Nobendu Mukerjee-study, Writing, Arabinda Ghosh-updated the manuscript and review, Jose M. Lorenzo & Kuldeep Dhama- Review & Editing, Abhijit Dey-design, review & editing.

Research registration Unique Identifying number (UIN)

1. Name of the registry:
2. Unique Identifying number or registration ID:
3. Hyperlink to your specific registration (must be publicly accessible and will be checked):

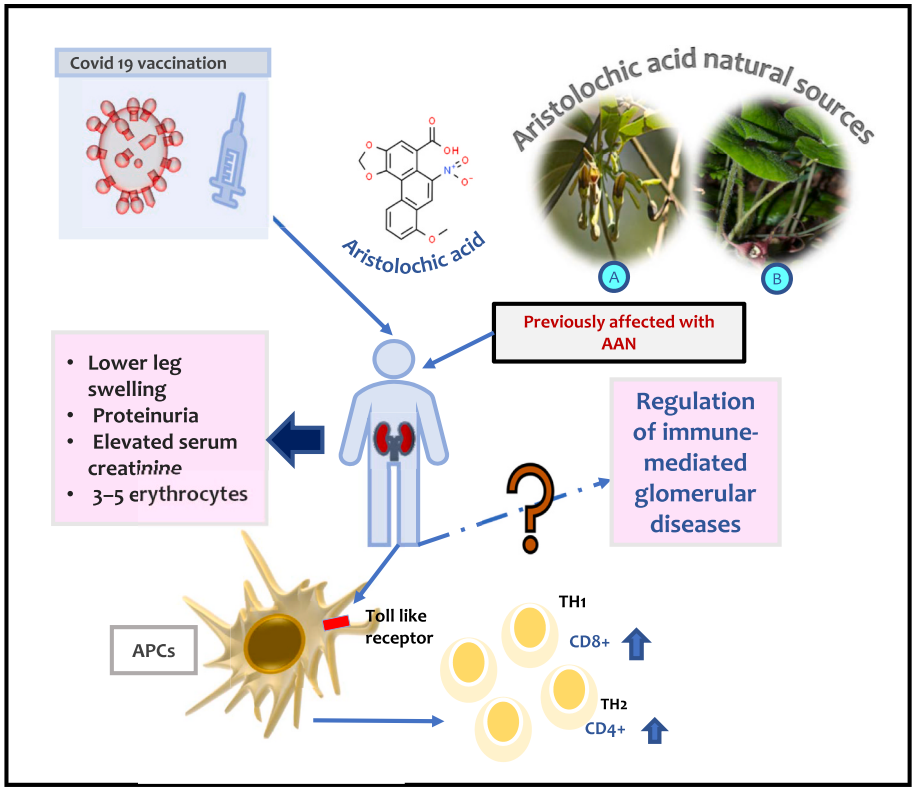

Fig. 1. Vaccination with COVID-19 may cause IgAN in patients with AAN. As a result of COVID-19 vaccination, $CD4^+$ and $CD8^+$ T cells in AAN patients are stimulated by proinflammatory cytokines, stimulating innate and adaptive immune responses. The most prevalent systemic signs lower leg swelling, proteinuria, and elevated serum creatinine, along with 3–5 erythrocytes in urine sediment.

Guarantor

I, Dr. Abhijit Dey (Corresponding author) am taking the full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

Data statement

N/A.

Provenance and peer review

Not commissioned, internally peer-reviewed.

Declaration of competing interest

N/A.

References

[1] https://www.prnewswire.com/news-releases/global-herbal-supplements-market-report- 2022-to-2027—industry-trends-share-size-growth-opportunity-and-forecasts-301582904.html.

[2] M. Heinrich, J. Chan, S. Wanke, C. Neinhuis, M.S. Simmonds, Local uses of Aristolochia species and content of nephrotoxic aristolochic acid 1 and 2—a global assessment based on bibliographic sources, J. Ethnopharmacol. 125 (1) (2009 Aug 17) 108–144, https://doi.org/10.1016/j.jep.2009.05.028.

[3] J. Scarborough, A. Fernandes, Ancient medicinal use of aristolochia: birthwort's tradition and toxicity, Pharm. Hist. 53 (1) (2011) 3–21.

[4] J. Ren, N.P. Rudemiller, Y. Wen, X. Lu, J.R. Privratsky, S.D. Crowley, The transcription factor Twist1 in the distal nephron but not in macrophages propagates aristolochic acid nephropathy, Kidney Int. 97 (1) (2020 Jan 1) 119–129, https://doi.org/10.1016/j.kint.2019.07.016.

[5] B. Jelaković, Ž. Dika, V.M. Arlt, M. Stiborova, N.M. Pavlović, J. Nikolić, J.M. Colet, J.L. Vanherweghem, J.L. Nortier, Balkan endemic nephropathy and the causative role of aristolochic acid, InSeminars in nephrology 39 (3) (2019 May 1) 284–296, https://doi.org/10.1016/j.semnephrol.2019.02.007. WB Saunders.

[6] A. Prasad, M. Prasad, SARS-CoV-2: the emergence of a viral pathogen causing havoc on human existence, J. Genet. 99 (1) (2020 Dec) 1–4, https://doi.org/10.1007/s12041-020-01205-x.

[7] M. Mokos, N. Bašić-Jukić, IgA nephropathy following SARS-CoV-2 vaccination in a renal transplant recipient with a history of aristolochic acid nephropathy, Ther. Apher. Dial. (2021 Nov 23), https://doi.org/10.1111/1744-9987.13765.

[8] S. Tsukamoto, H. Wakui, K. Azushima, T. Yamaji, S. Urate, T. Suzuki, E. Abe, S. Tanaka, S. Taguchi, T. Yamada, S. Kinguchi, Tissue-specific expression of the SARS-CoV-2 receptor, angiotensin-converting enzyme 2, in mouse models of chronic kidney disease, Sci. Rep. 11 (1) (2021 Aug 19) 1–2, https://doi.org/10.1038/s41598-021-96294-8.

[9] L. Wu, B. Wang, M. Zhao, W. Liu, P. Zhang, Y. Shi, C. Xiong, P. Wang, W. Sun, S. Chen, Rapid identification of officinal Akebiae Caulis and its toxic adulterant Aristolochiae manshuriensis Caulis (*Aristolochia manshuriensis*) by loop-mediated isothermal amplification, Front. Plant Sci. 7 (2016 Jun 20) 887, https://doi.org/10.3389/fpls.2016.00887.

[10] G. Hassen, G. Belete, K.G. Carrera, R.O. Iriowen, H. Araya, T. Alemu, N. Solomon, D.S. Bam, S.M. Nicola, M.E. Araya, T. Debele, Clinical implications of herbal supplements in conventional medical practice: a US perspective, Cureus 14 (7) (2022 Jul 15), https://doi.org/10.7759/cureus.26893.

[11] A. Dey, A.K. Hazra, A. Mukherjee, S. Nandy, D.K. Pandey, Chemotaxonomy of the ethnic antidote *Aristolochia indica* for aristolochic acid content: implications of anti-phospholipase activity and genotoxicity study, J. Ethnopharmacol. 266 (2021 Feb 10), 113416, https://doi.org/10.1016/j.jep.2020.113416.

[12] V. Romanov, T.C. Whyard, W.C. Waltzer, A.P. Grollman, T. Rosenquist, Aristolochic acid-induced apoptosis and G2 cell cycle arrest depends on ROS generation and MAP kinases activation, Arch. Toxicol. 89 (1) (2015 Jan) 47–56, https://doi.org/10.1007/s00204-014-1249-z.

[13] Y. Cheng, R. Luo, K. Wang, M. Zhang, Z. Wang, L. Dong, J. Li, Y. Yao, S. Ge, G. Xu, Kidney disease is associated with in-hospital death of patients with COVID-19, Kidney Int. 97 (5) (2020 May 1) 829–838, https://doi.org/10.1016/j.kint.2020.03.005.

[14] D. Wang, B. Hu, C. Hu, F. Zhu, X. Liu, J. Zhang, B. Wang, H. Xiang, Z. Cheng, Y. Xiong, Y. Zhao, Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China, JAMA 323 (11) (2020 Mar 17) 1061–1069, https://doi.org/10.1001/jama.2020.1585.

[15] H. Ji, J. Hu, G. Zhang, J. Song, X. Zhou, D. Guo, Aristolochic acid nephropathy: a scientometric analysis of literature published from 1971 to 2019, Medicine (27) (2021 Jul 7) 100, https://doi.org/10.1097/MD.0000000000026510.

[16] H. Askari, N. Sanadgol, A. Azarnezhad, A. Tajbakhsh, H. Rafiei, A.R. Safarpour, S. M. Gheibihayat, E. Raeis-Abdollahi, A. Savardashtaki, A. Ghanbariasad, N. Omidifar, Kidney diseases and COVID-19 infection: causes and effect, supportive therapeutics and nutritional perspectives, Heliyon 7 (1) (2021 Jan 1), e06008, https://doi.org/10.1016/j.heliyon.2021.e06008.

Tuyelee Das
Department of Life Sciences, Presidency University, 86/1 College Street, Kolkata, 700073, West Bengal, India

Nobendu Mukerjee
Department of Microbiology, Ramakrishna Mission Vivekananda Centenary College, West Bengal, 700118, India

Arabinda Ghosh
Microbiology Division, Department of Botany, Gauhati University, Gauhati, Assam, 781014, India

Jose M. Lorenzo
Centro Tecnológico de la Carne de Galicia, Adva. Galicia n° 4, Parque Tecnológico de Galicia, San Cibrao das Viñas, 32900, Ourense, Spain
Universidade de Vigo, Área de Tecnoloxía dos Alimentos, Facultade de Ciencias de Ourense, 32004, Ourense, Spain

Kuldeep Dhama
Division of Pathology, ICAR-Indian Veterinary Research Institute (IVRI), Izatnagar, 243122, Bareilly, Uttar Pradesh, India

Abhijit Dey*
Department of Life Sciences, Presidency University, 86/1 College Street, Kolkata, 700073, West Bengal, India

* Corresponding author.
E-mail address: abhijit.dbs@presiuniv.ac.in (A. Dey).