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Review Article

Taming the Fire of Nephrotoxic Botanicals

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Abstract

Criteria for diagnosing nephropathy and urothelial neoplasms induced by botanicals containing aristolochic acids (AAs) are well established. Highlights of recent research on AAs include mechanisms of AA intrarenal transport and metabolism and vigorous debate on whether AAs may also cause liver cancers. Many other botanicals may also cause renal injury, but a generalized framework for diagnosing botanical-induced kidney injury (BIKI) is lacking. Based on what we have learnt about the wide spectrum of phenotypes of BIKI attributed to AAs and a recently published standardized phenotypic framework of drug-induced kidney disease, we propose that BIKI may be categorized into six phenotypes (acute kidney injury, tubular dysfunction, glomerular disorders, nephrolithiasis, chronic kidney disease, and neoplasms) and four mechanistic types (A, predictable; B, idiosyncratic; C, chronic; and D, delayed). We call for international cooperation assembling a task force to develop, refine, and regularly appraise an online BIKI database, documenting botanical use, phenotypes, mechanisms, and levels of evidence. Once established, such a database may be linked with electronic patient records and pharmacovigilance channels to generate alerts, guide clinical decision-making, direct future research, and support evidence-based regulation of herbal medicines and education of healthcare professionals and the public. Finally, to prevent BIKI, we propose that a proactive approach integrating the triad of botanicals, users, and stakeholders will be needed.

Keywords: Adverse effects, database, herbal, kidney, mechanisms, phenotypes, prevention

Introduction

Botanicals are broadly defined as materials derived from plants and the term particularly refers to medicinal plants (herbs), herbal materials, herbal preparations, and finished herbal products that contain parts of plants as active ingredients and are used as herbal medicines or functional food. In past decades, globalization has accelerated exchanges of herbal traditions, and herbal medicines have gained popularity worldwide and become more important to the medical and pharmaceutical community, as well as to the public.[1,2] Also known as botanical medicine, phytomedicine, or phytotherapy, herbal medicines have deep cultural roots and long historic records of use in humans. These materials are arguably the most important part of traditional medicine.[3,4] Indeed, herbal medicines have some drug-like properties, are a rich resource and knowledge base for new drugs, and offer new options for unmet medical needs.[5,6] In keeping with this, regulators worldwide have increasingly approved and regulated herbal medicines as drugs.[7,8]

Access this article online

Quick Response Code:

Website: www.wjtcm.net

DOI: 10.4103/wjtcm.wjtcm_2_19

However, herbal medicines, and other traditional medicines, can be both friends and foes to the kidneys, as elegantly reviewed by Wojcikowski *et al*.[9,10] and most recently by Stanifer *et al*.[11] The US National Kidney Foundation has suggested renal patients to "avoid all herbal supplements," especially 17 potential nephrotoxic herbs and over 50 phosphate-or potassium-rich herbs.[12] While acknowledging the potential for harm, we feel that there is potential clinical and scientific value for herbal medicines in prevention and treatment of acute kidney injury (AKI)[13] and chronic kidney disease (CKD),[14,15]

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Received: 24-08-2018, **Accepted:** 04-01-2019

How to cite this article: Holden F, Amin V, Kuek D, Kopp JB, Hendry BM, Xu QH. Taming the fire of nephrotoxic botanicals. World J Tradit Chin Med 2019;5:151-63.

including drug-induced nephrotoxicity and that further research is warranted.[16] For example, in a large cohort study of 24,971 CKD patients, use of Chinese herbal medicines was associated with a significantly better prognosis,[17] and GQ5, a Smad3 inhibitor of botanical origin, inhibited renal fibrosis in animal models.[18] On the other hand, as major organs for excretion of drugs and toxins, kidneys feature extensive vasculature, rich blood flow, large endothelial surface area, active tubular transport and metabolism, drastic changes of osmosis, pH, and oxygen tension[19-21] and are particularly susceptible to injury induced by drugs and toxins, including herbal toxicants. Thus, caution must be exercised to avoid unnecessary exposure of patients, especially those with kidney diseases, to herbal medicines and other botanical materials.

Guided by the consensuses of the GP-TCM consortium 2009-2012,[22-25] an EU-funded European-Chinese collaboration dedicated to good practice in research of traditional Chinese medicine (TCM), the corresponding author of this paper has offered medical students at King's College London three Student-Selected-Component (SSC) modules on the opportunities and challenges botanicals bring about. One of such SSC modules is designed for Year-3 graduate students to review on nephrotoxic botanicals. The SSC reviews clearly pointed to aristolochic acid nephropathy (AAN) and AA-induced neoplasms affecting the kidneys and the other parts of the urinary tract as the most established form of botanical-induced kidney injury (BIKI). This has been elegantly reviewed by Debelle *et al*., highlighting AA-containing species, herbs adulterated or contaminated by AA-containing species, and the worldwide spread of this problem.[26] Yang *et al*. reviewed the variable clinical presentations of AAN,[27] and Gökmen *et al*. summarized the epidemiology, diagnosis, and clinical management.[28] More recently, AAN and AA-induced urothelial cancer and related mechanisms were updated by Jadot *et al*.[29] and Baudoux and Nortier.[19] Readers are recommended to these excellent papers for details.

BIKI, however, goes beyond AAN and AAs-induced neoplasms, as reviewed by a number of experts and summarized in Table 1. Most of these peer-reviewed papers have tables listing a range of botanicals which might be "associated" with nephrotoxicity, but they often suffer from obscure evidence for causal relations and are complicated with varying phenotypic and mechanistic frameworks. Building on databases, guidelines, and publications of the GP-TCM project and the aforementioned reviews, we have conducted further reviews to inform the best strategies for preventing BIKI. We searched PubMed using the following searching strategies: ("herbal medicine" [MeSH Terms] OR traditional medicine OR phytomedicine OR phytotherapy OR Botanical* OR aristolochi*) AND (kidney* OR renal) AND (adverse effects OR side effects OR toxicity OR nephrotoxic*), and this was supplemented by more targeted literature search on specific issues. For example, "aristolochic" was searched in PubMed, and all titles published in the recent 5 years were gone through to identify noteworthy developments on AAN and AAs-induced neoplasms. Moving forward, we propose three keys: (i) Learning from the lessons of AAN and AAs-induced neoplasms; (ii) Building a reliable database; and (iii) Developing an integrative approach to prevention.

Learning from the Lessons of Aristolochic Acid Nephropathy and Aristolochic Acid-Induced Neoplasms

AAN and AA-induced neoplasms are not only the most well-established BIKI but also an excellent example to illustrate the complexity of BIKI. It can be caused by ingestion of food or drugs, knowing or unknowingly, with a range of phenotypes, including AKI, CKD, tubular disorders, and neoplasms. AAs and analogs are mainly contained in the *Aristolochia* and Asarum genera. According to a search of Medicinal Plant Names Service searching portal, the genus *Aristolochia* alone has >400 species, of which 103 have documented medicinal use worldwide and the *Asarum* genus has 155 species and 33 have documented medicinal use historically. In fact, the first use of an *Aristolochia* species − to stimulate the expulsion of the placenta during childbirth − was responsible for coining the name "*Aristos lokos*" or "excellent delivery," while *Asarum* plants were also widely used in Europe for the treatment of gout and arthralgia.[19]

Not all *Aristolochia* and *Asarum* plants are equally dangerous. In population-based case–control studies from Taiwan, Lai *et al*. established consumption of herbal medicines containing Guan Mu Tong (roots of *Aristolochia manshuriensis*) and Guang Fangchi (roots of *Aristolochia fangchi*) but not Xi Xin (roots of *Asarum heterotropoides*) and Ma Dou Ling (dried fruits of *Aristolochia contorta* or *Aristolochia debilis*), as dose-dependent independent risk factors of developing end-stage renal disease (ESRD) and urothelial neoplasms.[30,31] In these reports, evidence is the strongest for Guan Mu Tong to cause AAN and urinary tract cancers, followed by Guang Fangchi. Accumulative ingestion of >61–100, 101–200, and >200 g Guan Mu Tong (*A. manshuriensis*) significantly increased odds ratio (OR) of ESRD (1.47, 2.14, and 5.82), with accumulative ingestion of Guan Mu Tong >200 g on a par with other ESRD risk factors such as diabetes (OR 4.90) and hypertension (OR 6.95).

In the aforementioned study by Lai *et al*., ingestion of 1–30 and 31–60 g Guan Mu Tong was not significantly associated with increased ESRD risk at the population level. However, such data must be explained with care at the individual level. In light of variations in AA analog concentrations in different herbal preparations and genetic factors underlying individual susceptibility to AAs, a "safe dose" of AA analogs and AA-containing botanical products cannot yet be established despite the apparent dose dependency of AAN. For example, Guan Mu Tong contains about 25% more AAs than Guang

Table 1: Recommended readings: Published reviews on botanical-induced kidney injury

Review	Summary of contents and resources provided
Isnard Bagnis C, Deray G, Baumelou A, Le Quintrec M, Vanherweghem JL. Herbs and the kidney. Am J Kidney Dis 2004;44:1-11.	An overview of botanical nephrotoxicity and BIKI A summary to the clinical manifestations of BIKI, including tubular necrosis, acute interstitial nephritis, Fanconi syndrome, hypokalemia or hyperkalemia, hypertension, papillary necrosis, chronic interstitial nephritis, nephrolithiasis, urinary retention and cancer of the urinary tract Warning that some herbal medicine and impurities might affect blood pressure, drug and potassium blood levels and coagulation, induce rhabdomyolysis in renal patients; and A series of websites for further information about BIKI
Wojcikowski K, Johnson DW, Gobé G. Medicinal herbal extracts - Renal friend or foe? Part one: The toxicities of medicinal herbs. Nephrology (Carlton) 2004;9:313-8.	Three possible causes of BIKI: Phytotoxins such as AAs, impurities, herb-drug interactions Warning that chronic types of BIKI caused by insidious damage is a concern because chronic nephrotoxicity of many herbs has not been rigorously tested
Luyckx VA, Naicker S. Acute kidney injury associated with the use of traditional medicines. Nat Clin Pract Nephrol 2008;4:664-71.	Focused discussions on pathologies, manifestations, and mechanisms underlying AKI associated with traditional medicines, for example, ATN, AIN, hepatorenal syndrome, rhabdomyolysis, renal tubular acidosis, Fanconi syndrome, diabetes insipidus, papillary necrosis, transplant rejection, renal cysts, kidney stones and urinary tract obstruction, glomerular injury, urothelial malignancy, as well as signs of chronic lesions such as renal fibrosis Two online supplementary tables enlisting traditional medicines associated with AKI and CKD, respectively
Baudoux T, Nortier JL. Nephrotoxicity of herbal products. In: Toxicology of Herbal Products. Cham, Switzerland: Springer International Publishing; 2017. p. 307-44.	Nephrotoxicity of herbal products retrieved from English literature categorized into nine systemic, renal and urological syndromes, i.e., hypertension, ATN, AIN, tubular functional disorders (Fanconi syndrome), papillary necrosis, chronic interstitial nephritis, urinary retention, urolithiasis, and urothelial cancer Five tables enlisting case reports on BIKI associated with intrinsic botanical nephrotoxicity, herbal misuse, contamination of herbal products by drugs and heavy metals, herbal misidentification and adulteration, and herbal-drug interaction, respectively; and An introduction to the strengths and limitations of *in silico, in vitro, in vivo*, and omic methodologies for assessing renal toxicity
Jha V. Herbal medicines and chronic kidney disease. Nephrology (Carlton) 2010;15 Suppl 2:10-7.	A summary of 12 groups of plants associated with CKD, including those containing AAs, nordihydroguaiaretic acid, ephedrine, djenkolic acid, oxalic acid, glycyrrhizin, salicin, yohimbine, anthraquinone, arabinogalactan, and those contaminated by heavy metals
Xu XL, Yang LJ, Jiang JG. Renal toxic ingredients and their toxicology from traditional Chinese medicine. Expert Opin Drug Metab Toxicol 2016;12:149-59.	A summary to nephrotoxicants found in herbs used in TCM, including nephrotoxic AAs, alkaloids, anthraquinones, flavonoids, and glycosides
Stanifer JW, Kilonzo K, Wang D, Su G, Mao W, Zhang L, *et al*. Traditional medicines and kidney disease in low- and middle-income countries: Opportunities and challenges. Semin Nephrol 2017;37:245-59.	A review on the medicinal use of botanicals in sub-Saharan African countries, China, India, and Latin American countries Examples to illustrate the similarities and differences of the herbal traditions and outstanding problems, highlighting low levels of evidence on efficacy and nephrotoxicity of herbal medicines

ATN: Acute tubular necrosis, AIN: Acute interstitial nephritis, CKD: Chronic kidney disease, TCM: Traditional Chinese medicine, AAs: Aristolochic acids, BIKI: Botanical-induced kidney injury, AKI: Acute kidney injury

Fangchi, with Xi Xin containing only 0.5%–2% of the AAs of Guang Fangchi. These differences could explain why the former is more potently nephrotoxic and carcinogenic and why the latter does not have observable toxicity at the population level. Interestingly, cumulative ingestion of 1–1000 g Xi Xin was consistently associated with significantly reduced risk of ESRD (OR: 0.41–0.79). Thus, although Guan Mu Tong and Guang Fangchi have been banned for medicinal use worldwide, Ma Dou Ling and its corresponding aerial parts known as Tian Xian Teng, which has 10-times higher AA-I content than that of Xi Xin, remain legal herbal drugs in China, carrying warnings on its AA content and potential nephrotoxicity. For Xi Xin, despite the requirement for legal AA-I levels, it does not carry a nephrotoxic warning in the Chinese Pharmacopoeia 2015. However, water decoctions are 10–40-fold less efficient than methanol to extract AA-I from Xi Xin. Furthermore, the roots of the plant – the legal portion of the plant for medicinal use – contain 2–4-fold less AA-I amount than its aerial portions. Thus, use of the wrong plant portions including whole plant and altered extraction methods (e.g., alcoholic extract) could still lead to poisoning.[32]

AAs have many naturally occurring analogs. It has been believed that AA I is the most toxic, followed by AA II, AA VIIIa, and AA Ia.[33] A metabolomic analysis was carried out on 43 medicinally used *Aristolochia* species. Compounds AA I and AA II were found to be the most common AA analogs found in these extracts. AA IV, aristolactam I, and aristolactam BI were also widespread. The cytotoxicity and genotoxicity of 28 *Aristolochia* extracts were measured in HK-2 human kidney proximal tubular cells. Contrary to the prediction, no correlation was found between the amounts of AA I or AA II and extract cytotoxicity against HK-2 cells. The genotoxicity

and cytotoxicity of the extracts could be linked to their contents of aristolactam BI, AA D, and AA IIIa. These results undermine the assumption that AA I and AA II are exclusively, or even chiefly, responsible for the toxicity of AA-containing species. Other analogs need to be considered as nephrotoxic agents.[34] In this context, it should be noted that AA metabolites such as aristolactam I nitrenium ion, which readily forms AA-DNA adducts, are associated with increased tumor risk.[29]

Intriguingly, individuals with comparable AA exposure differ greatly in developing AAN. For example, of the Belgian patients treated with the same AA-containing slimming regimen, only 2%-10% experienced AAN and those affected had varying rates of disease progression.[35,36] Similarly, in the area where Balkan nephropathy is endemic, only 3%–7% of the population chronically exposed to AAs in food contaminated by seeds of *Aristolochia clematitis* developed AAN.[37]

Interindividual differences in intrarenal AA transport, AA-metabolizing enzymes, and/or defense mechanisms against AAN may, at least in part, explain individual differences in resistance and susceptibility to AAN and AA-induced neoplasms. These differences could be due to genetic variations in individuals or various environmental factors that modulate enzymatic activity. Identifying these factors could potentially help in identifying vulnerable patient groups and guide treatment. For example, proximal tubular epithelial cells are the most sensitive to AAs. In these cells, organic anion transporter 1 (OAT1) plays a major role in absorbing AAs, and in HEK293 cells, an OAT1 inhibitor significantly reduced the level of AA I accumulation, while AAs induce increased apoptosis in OAT1-transfected HEK293 cells.[38] More than 50 single nucleotide polymorphisms have been identified in the coding region of OAT1,[39] and it would be interesting to examine if expression levels, activities and genetic variations in the OAT1 gene, and other genes involved in intrarenal AA transport affect susceptibility to AAs.

Further, cytochromes P450 (CYP) A1 and A2 enzymes are responsible for both reductive activation and oxidative detoxification of AAs. AA I is reduced at low oxygen concentrations by CYP1A1 and 1A2 and oxidized under aerobic conditions.[40] As such, oxygen concentration in tissues may account for the differences in cytotoxicity of AAs. CYP genes are differentially expressed in males and females, at least in part due to sexual hormones, and also exhibit genetic polymorphisms. Furthermore, the activity of CYP1A1 and CYP1A2 can also be induced or inhibited by various compounds that naturally occur in fruits and vegetables.[41] For example, baicalin, a flavone glycoside, has been shown to induce Cyp1a1 and Cyp1a2 expression in mice and attenuate AA-induced renal injury.[42] Therefore, genetic and environmental factors that can modulate CYP1A1 and CYP1A2 activities must be further studied to understand individual susceptibility and resistance to AAN and carcinogenesis. Other enzymes that play a role on AA metabolism and susceptibility to AAs-induced BIKI include glutathione S-transferase theta 1,[43,44] NAD(P)H quinone oxidoreductase,[45-49] sulfotransferase 1A1,[50,51] and cyclooxygenase/prostaglandin H synthase.[52]

AAs and its analogs also have the potential to damage various tissues.[53] In zebrafish embryos, AAs induce inflammation-mediated heart failure.[54] In dogs, AA I can induce premalignant alterations in liver.[53] In rats, AAs exhibit significant toxicity to both liver and kidneys[55] and induce mutation of the H-Ras proto-oncogene in stomach.[56] Based on a signature A: T > T: A nucleotide substitutions, AAs and their derivatives were recently implicated in liver cancers in Taiwan and throughout Asia,[57] but this study was widely criticized due to uncontrolled confounding factors and nonspecificity of A: T > T: A nucleotide substitution as a marker of AA exposure.[58] In a later report from mainland China, similar mutation was not commonly observed in patients with hepatic carcinoma.[59] and indeed, genes regulate proliferation and carcinogenesis in a highly tissue-specific manner.[60] Nonetheless, it is clear that AAs induce nephrotoxicity and cancers of the urinary tract, and exposure to AAs from all sources should be avoided.

Building a Reliable Database

Further complexity of BIKI lies in the fact that AAs and their analogs are far from the only botanical compounds that cause BIKI, and the phenotypic and mechanistic spectra of BIKI go far beyond AAN and AAs-induced neoplasms. With regard to the reviews summarized in Table 1, each contains excellent expert opinions on one aspect of BIKI, but they all more or less are limited in the following ways: (i) nonstandardized phenotypes; (ii) often unknown mechanisms; and (iii) often obscure confidence levels of causality. To address these problems, at the 16th Consortium for Globalization of Chinese Medicine Meeting held in Guangzhou, China, in August 2017, we proposed that an integrated database, linking botanicals and usage, phenotypes, mechanisms, as well as evidence and confounding factors, is desperately needed [Figure 1]. If such a database is established, the following will be possible: electronic health and medical history can be linked with nephrotoxicity databases to generate alerts to subscribers, as recently proposed by Goldstein;[61] a consensus framework for phenotypes, mechanisms, and evidence will help with evidence-based regulation;[62] and equally important, it will guide future research for better evidence. Herein, we interpret our proposal as follows.

Botanicals and usage

As we have learnt from AAN, whether BIKI occurs may depend on many variables: (1) whether particular species and plant parts are used, (2) whether they are processed and manufactured to meet quality standards, (3) whether their quality is compromised by contamination, adulteration, or expiry, (4) whether they are prescribed by properly trained practitioners to the right person based on right diagnoses, (5) whether the dosage and duration are appropriate, and (6) whether adverse herb–herb interaction and herb–drug interaction exist, etc. In TCM, for example, herbal medicines

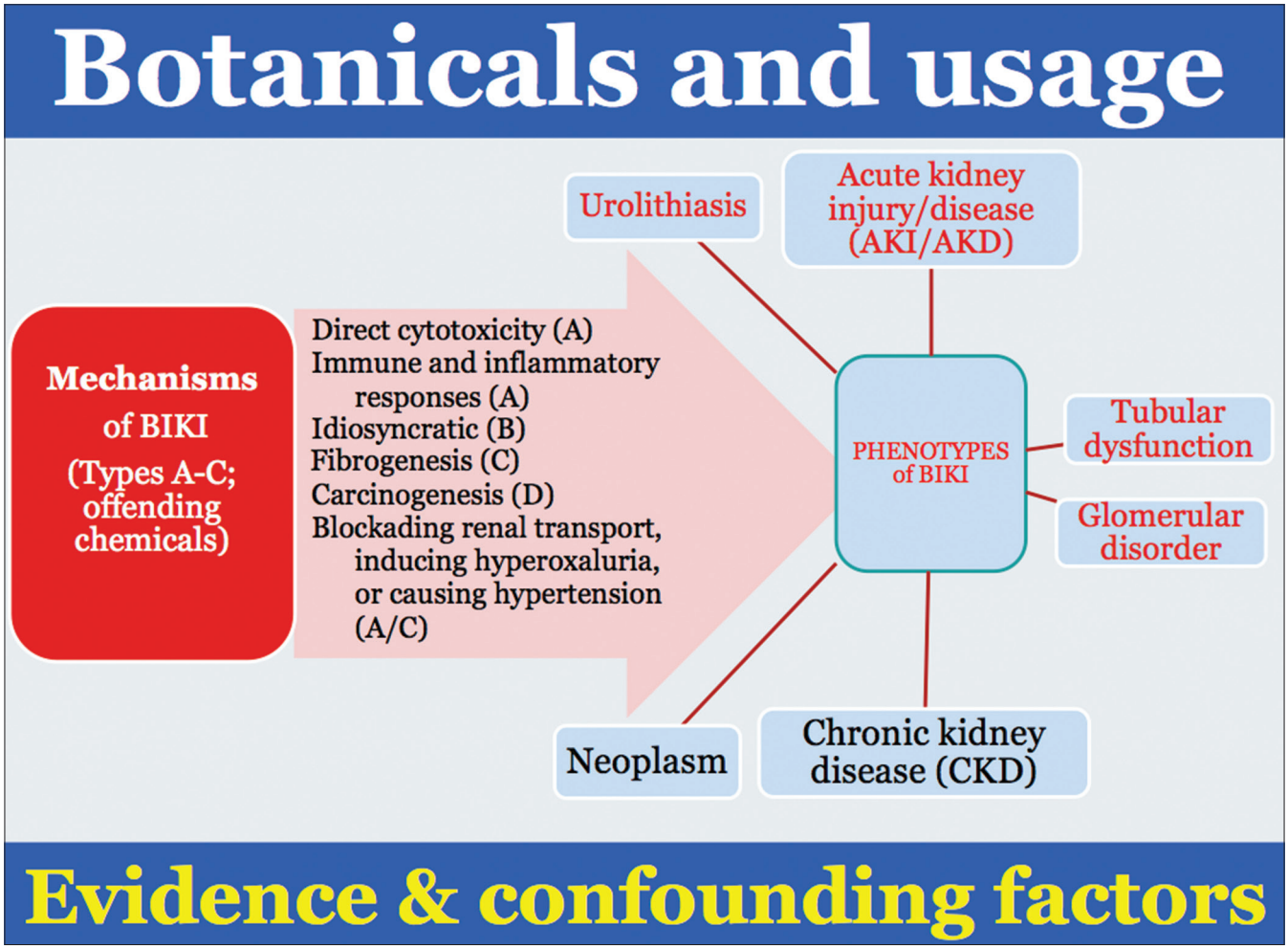

Figure 1: An integrated database of BIKI and its expected main elements. Phenotypes in red fonts are those proposed by Mehta *et al*. for drug-induced kidney disease; those in black fonts are additional ones that we propose to add

should be prescribed based on TCM diagnosis and adjusted as the patients' clinical manifestations change, but they are often taken without proper guidance by qualified TCM practitioners. Thus, proper documentation of relevant information about botanicals and usage (including traditional use) is the first step of building a useful database on BIKI.

Phenotypes

Except for the particular cases of AAN and AAs-induced upper urinary tract urothelial cancer (UUC), no BIKI diagnostic framework is universally accepted. In the past decade, the International Serious Adverse Events Consortium has become a leading force in standardizing diagnosis of drug-induced adverse effects and understanding the underlying genetic mechanisms. As a not-for-profit biomedical research organization, the consortium comprises academic institutions, pharmaceutical companies, and biomedical charities and receives scientific and strategic input from the US Food and Drug Administration (FDA) and other international regulatory bodies. A panel of nephrologists and pharmacists from five different countries recently defined four standardized phenotypes of drug-induced kidney disease (DIKD), i.e., AKI, tubular dysfunction, glomerular disorders, and nephrolithiasis, along with primary and secondary clinical criteria to support the phenotype definition and a time course based on the Kidney Disease Improving Global Outcome (KDIGO)/AKI Network definitions of AKI and CKD.[63] These phenotypes have provided a consistent framework to evaluate drug nephrotoxicity across various settings and could be borrowed for diagnosis of BIKI, but they failed to include some important phenotypes of BIKI, such as CKD and UUC, which are well-established phenotypes of AA-induced BIKI.[27] Thus, we propose that we modify the framework into six phenotypes, by adding CKD and neoplasms. The six phenotypes of BIKI will allow mixed phenotypes, stratification, and addition of new phenotypes in the future.

Acute kidney injury

This phenotype is based on the KDIGO definition,[64] with minor modification.[63] AKI encompasses a rise in serum creatinine levels and mainly includes botanical-induced acute tubular necrosis (ATN) and acute interstitial nephritis (AIN) although prerenal, postrenal, and other intrarenal causes are

also possible.[63] Although the term acute renal failure has largely been replaced by AKI,[65] the former term is still used in reference to very serious AKI for which renal replacement therapy is needed. Indeed, the Risk, Injury, and Failure; and Loss of kidney function; and End-stage kidney disease (RIFLE) criteria and its pediatric version RIFLE recommend to grade AKI into different stages, and diagnosis at the "Risk" stage can be made before "Injury," "Failure," "Loss," and "End-stage" of renal failure are established. For specificity purposes, the phenotypic criteria proposed by Mehta *et al*. are stricter.[63] For screening, alerting, and preventing purposes, however, whether AKI induced by botanicals should be proposed at earlier stages of AKI deserves further investigation. In view of the evolving definition of AKI and the difficulty in establishing causality, the true prevalence of BIKI manifesting as AKI remains largely unknown. In the developing countries, however, it was reported that folk remedies accounted for up to 35% of cases of AKI.[66] We list some best-known examples of botanicals associated with AKI in Supplementary Table 1. These include AA-containing species, nephrotoxic flavonoid-containing species, triptolide-containing species, *Aloe vera, Aloe ferox*, *Callilepis laureola* (Impila), *Teucrium polium, Artemisia absinthium* (wormwood), and *Uncaria tomentosa or U. guianensis* (cat's claw), etc.

Nephrolithiasis

Renal calculi develop most commonly from calcium oxalate.[67,68] Calculi provoke symptoms and signs such as renal colic, nausea, vomiting, hematuria, pyuria, pyrexia, and dysuria and may cause ureteric obstruction and reduced renal function. Some botanical compounds can precipitate as crystals, depending on their urinary solubility. Patients may be asymptomatic, or this may lead to isolated crystalluria or stones. To classify the nephrolithiasis phenotype, imaging such as ultrasound should be performed to definitively visualize a stone, with or without obstruction. In addition, due to the naturally high incidence of calculi in the population, when conducting investigations, it is imperative to establish the temporal relationship of the suspect botanical and analyze calculi composition. Furthermore, there should be no prior history of calculi as this may influence the clinical interpretations made regarding the particular botanical.[63] This phenotype may induce AIN and/or renal tubular acidosis syndromes, and obstructive calculi could induce AKI or CKD.[63] Of note, partial obstruction and unilateral obstruction could damage renal function without leading to a rise in serum creatinine due to the strong renal function reserve. If there is nonobstructive nephrolithiasis, then ultrasound should detect the presence of stones, or urinalysis should detect crystals unless the drug has been discontinued for some time.[63] Many factors can influence the formation of kidney stones but in particular, hyperoxaluria and hypercalciuria are known to play a significant role.[63] Botanicals associated with calcium oxalate calculi and nephrolithiasis include cranberry (*Vaccinium* species) juice, rhubarb (*Rheum officinale*), star fruit (*Averrhoa carambola*), Ephedrine (a compound isolated from *Ephedra sinica),* Guaifenesin (a constituent of *Guaiacum officinale*), etc., [Supplementary Table 2].

Tubular dysfunction

Botanicals may lead to tubular dysfunction ranging from isolated dysfunction such as phosphate wasting to more generalized damage causing acquired Fanconi syndrome, diabetes insipidus, or proximal tubular acidosis. Mehta *et al*. included the tubular dysfunction phenotype in their framework of DIKD. It is characterized by abnormal urinary losses of glucose, phosphate, potassium, magnesium, water, and tubular proteins and secondary abnormalities such as changes in serum electrolytes, pH, and bicarbonate. The latter must be also present to improve specificity.[63] AA-containing botanicals are known to cause tubular dysfunction, which can manifest as Fanconi syndrome.[69-72] Fanconi syndrome involves dysfunction of the proximal renal tubule, leading to urinary loss of glucose, amino acids, phosphate, uric acid, and bicarbonate. Other botanicals associated with tubular dysfunction include *Cleistanthus collinus* and diuretic Juniper berries (*Juniperus communis*), dandelion (*Taraxacum officinale*), asparagus root *(Asparagus officinalis),* lovage root (*Levisticum officinale*), parsley (*Petroselinum crispum*), stinging nettle leaf (*Urtica dioica*), etc., [Supplementary Table 3].

Glomerular disorders

Botanicals may induce glomerular injury, with patients presenting with hematuria, proteinuria, and associated urinary sediment abnormalities. Based on the DIKD framework of Mehta *et al*., primary criteria should include substantial proteinuria and a kidney biopsy demonstrating glomerular disease that can be plausibly associated with a particular botanical and not with another disease.[63] Yellow oleander (*Cerbera thevetia*) was reported to cause hematuria and proteinuria, suggestive of glomerular injury.[66] Animal studies demonstrated that feeding yellow oleander seeds to rats induced glomerular endothelial proliferation and glomerular hypercellularity. Further, both human and animal kidneys have displayed ATN postmortem,[73-76] indicating tubular toxicity. In addition, arsenic-contaminated bladderwrack (*Fucus vesiculosus*) was reported to induce mesangial proliferation, interstitial fibrosis, and tubular degeneration, manifesting proteinuria and hematuria.[77]

Chronic kidney disease

Botanicals can induce kidney injury over a long period of time. For example, *Glycyrrhiza glabra* and ephedrine-containing *Ephedra* spp. or herbal mixtures of ephedrine-containing components may induce hypertension, a risk factor for CKD progression.[78,79] However, AAN is probably the best example demonstrating that BIKI can manifest either acutely or chronically.[27] An observational study which involved 300 individuals showed that AAN has variant phenotypes of BIKI, including AKI, tubular dysfunction, and CKD, with the latter being the most common clinical manifestation. The clinical subtypes were associated with cumulative doses and time course of AA consumption, for example, those exposed

to the lowest dose but for the longest period of exposure to AAs.[27] One such phenotype of AAN is found in Balkan endemic nephropathy, a chronic tubulointerstitial kidney disease found in farming villages in Bulgaria, Romania, and Serbia.[80] It is characterized by an asymptomatic onset with a slow progression to ESRD and increased frequency of UUC. It was first suggested that environmental exposure to AA may be a cause of Balkan endemic nephropathy when Ivic found wheat flour was contaminated with *A. clematitis* seeds.[81] Subsequently, aristolactam-DNA adducts and hallmark A: T > T: A transversions have been found in renal cortical and urothelial malignant tissue of patients with Balkan endemic nephropathy.[81-85] A storage protein called dioscorin in *Dioscorea villosa* (wild yam) increases the expression of cytokines involved in renal fibrosis, such as transforming growth factor (TGF)- beta 1.[86-88] When administered to rats, *D. villosa* increases expression of renal TGF-ß1 and induces renal fibrosis and hepatic inflammation after 28 days.[86] Furthermore, *Leonurus japonicus* (known as Yimucao in TCM) was reported to have *in vitro* profibrotic activities[89] and induce renal fibrosis in animal models, and its toxicity was reduced when used in TCM formulae.[90,91]

Renal and urothelial neoplasms

After the original reports of AAN, a body of evidence emerged, associating UUC with the consumption of AA-containing botanicals,[92-95] highlighting that BIKI can also manifest with renal or urothelial neoplasms. In a study, 4 out of 10 patients with AAN had a multifocal high-grade carcinoma *in situ,*[96] and this has been confirmed in larger studies of patients with AAN, which show that the risk for urothelial neoplasms is associated with doses of *A. fangchi.*[97] A similar rate of UUC was reported in a 15-year follow-up study along with a rise in the incidence of late-onset bladder tumors.[98,99] Studies in Taiwan have reported a very high incidence of UUC which is also associated with CKD[100] and a marked dose-dependent relationship between the ingestion of AA-containing botanicals and the risk of UUC.[31] AA exposure has been widely implicated in the development of UUC. Their carcinogenic effects have been well described with their ability to induce A: T > T: A transversions in the gene TP53.[101] This transversion signature is also present at the genome-wide level.[102,103] However, an association between AA exposure and renal cell carcinomas (RCC) has not been as widely explored. A whole-genome sequencing study of RCCs found that 12 out of 14 Romanian RCC cases demonstrated high rates of A: T > T: A transversions. In contrast, this mutational signature was absent in 80 other studied cases diagnosed in Europe.[104] In addition, the nonmalignant renal cortical tissue from the 14 Romanian cases studied did not display the hallmark histological features of AAN such as interstitial fibrosis or tubular atrophy. Therefore, these results triggered a further study to determine whether Aristolactam-DNA adducts were present in nonmalignant renal cortical tissue samples.[105] A similar level of DNA adducts was found in the 14 Romanian cases to the renal cortical tissue of patients with UUC in Taiwan and the Balkans,[105,106] and additionally, the proportion of A: T > T: A mutations positively correlated with the number of DNA-adducts.[105] Other studies have found that the RCC tissue samples of 5 of 8 patients with Balkan endemic nephropathy displayed the A:T > T:A transversion mutational signature. This signature was missing in control samples of RCCs from patients of non-Balkan endemic regions.[107]

Mechanisms

More than a quarter century ago, Huxtable enlisted a series of factors predisposing to intoxication from the use of herbs. These include the following: misidentification of a plant; the unknown or ignored toxicity of a correctly identified plants; difficulties in identifying chopped, processed herbs, or plant mixtures; persistent use of a toxic plant; variability in toxic plant constituents; problems of nomenclature; adulteration and the difficulty in establishing the chronic toxic potential of a plant; certain human populations at higher risk of intoxication, including chronic users, those consuming large amounts or a great variety, the very young, fetuses, the elderly, the sick, the malnourished and those on long-term medication, and certain ethnic groups; and certain plant toxins with gender-selective action.[108]

Much information surrounding BIKI remains unknown. To be pragmatic, however, BIKI can be divided into the following four types based on the classification of drug adverse effects by Edwards and Aronson:[109] (i) type A, which are attributable directly to the toxicity and properties of the botanicals themselves, thus predictable and often dose dependent; (ii) type B, which are attributable to personalized responses to botanicals, thus idiosyncratic and often not dose related or predictable by pharmacology; (iii) type C (chronic), which have cumulative effect; and type D, which have delayed onset and are carcinogenic and genotoxic. Of note, types B, C, and D are difficult to be noticed and established.

As illustrated by the case of AAN, identifying offending compounds has a critical importance in mechanistic studies of botanicals. Biologically, BIKI mechanisms can be further attributed to cytotoxicity, immune and pro-inflammatory responses, fibrogenesis, carcinogenesis, and blockade of renal transport, inducing hyperoxaluria and causing hypertension. Cytotoxicity can be due to regulated cell death mechanisms, including pyroptosis, apoptosis, and necroptosis,[110] and un-programmed necrosis, which all play important roles in inflammation,[111] which in turn play important roles in injury and repair. While botanical-induced apoptosis is most studied, roles for other types of cell death in BIKI remain elusive and deserve further studies. Supplementary Table 4 summarizes the current state of knowledge of BIKI biological mechanisms.

Evidence and confounding factors

Currently, many people including professionals use the internet to find medical information. Although practical, this can be misleading. Some websites[112,113] and earlier papers[114] labeled tens of herbs as "nephrotoxic," but many provided no source of information and supporting evidence and some could be due to adulteration or contamination. For example,

"Chaihu" (*Bupleurum chinense* roots) has been labeled as "nephrotoxic," but we could not find evidence in support of this claim. Indeed, "Chaihu" adulteration by nephrotoxic *A. manshuriensis* roots has been recently reported.[115] Senecionis Scandentis Herba (Qianliguang, the aerial portion of *Senecio scandens*) has also been listed as "nephrotoxic" but evidence supporting this claim is lacking; indeed, oral administration of an aqueous extract of the herb, 225, 450, and 900 mg/kg/d, for 90 days was reported to increase serum creatinine, potassium, and chloride in some rats, without changes in blood urea nitrogen levels, gross renal histology, urinary volume, urinary glucose, bilirubin, ketone body, specific gravity, occult blood, pH, protein, urobilinogen, nitrite, and leukocyte levels.[116] These findings suggest that the agent might affect bodily metabolism and/or impair renal tubular function. Thus, although the phytochemistry, pharmacological, and hepatotoxic properties of this pyrrolizidine alkaloid-containing herb are well documented,[117] whether it is nephrotoxic remains obscure.

Evidence of BIKI is often provided by case reports, which do not readily establish causality. Furthermore, a proportion of the evidence for BIKI mechanisms comes from animal or *in vitro* studies, which need to be carefully interpreted in terms of their clinical relevance. Thus, huge challenges often exist when assessing causal relations, in view that there are no internationally agreed standards or criteria for assessing causality in individual cases. Thus, we will restrain from labeling specific botanicals as "nephrotoxic" or any links as "causal" or "non-causal." Nonetheless, we do think it important to compare and refine existing algorithms[118,119] and to develop new ones for calculating causality scores for BIKI, which should be based on accumulating evidence and should indicate the likelihood of any causal BIKI.

Evidence from human cases is likely confounded by various factors. These include the presence of chronic conditions such as diabetes and hypertension, genetics and family history, diet, medication history, and access to healthcare. All of these may influence the mechanisms, pathways, progression, and/or treatment of BIKI.

One confounding factor particularly worth considering is whether it is the botanical itself causing nephrotoxicity or its adulterants and contaminants, for example, heavy metals and pesticides. For example, a case report stated that Bladderwrack (*Fucus vesiculosus*), a brown seaweed from the *Fucaceae* family, induced diabetes insipidus and tubular dysfunction after 3 months daily consumption.[77] The researchers found that the preparation was contaminated with high levels of arsenic,[77] and therefore, its pathogenesis is likely associated with the contamination of kelp preparations with arsenic and other heavy metals, due to growth in polluted waters.[120,121] Other case reports have described contamination of herbal products with cadmium leading to renal tubular dysfunction.[122] However, the degree to which cadmium was completely responsible was questioned, highlighting the difficulties in elucidating whether injury is due to contaminants, the plant itself, or a combination of the two with a preparation generating a dangerous interaction. This may lead to certain botanicals being misreported as nephrotoxic in the literature.

Developing an Integrative and Proactive Approach to Prevention

An integrative approach

In contrast to fire, which can be stopped when any side of the oxygen-fuel-heat triangle is removed, BIKI can be

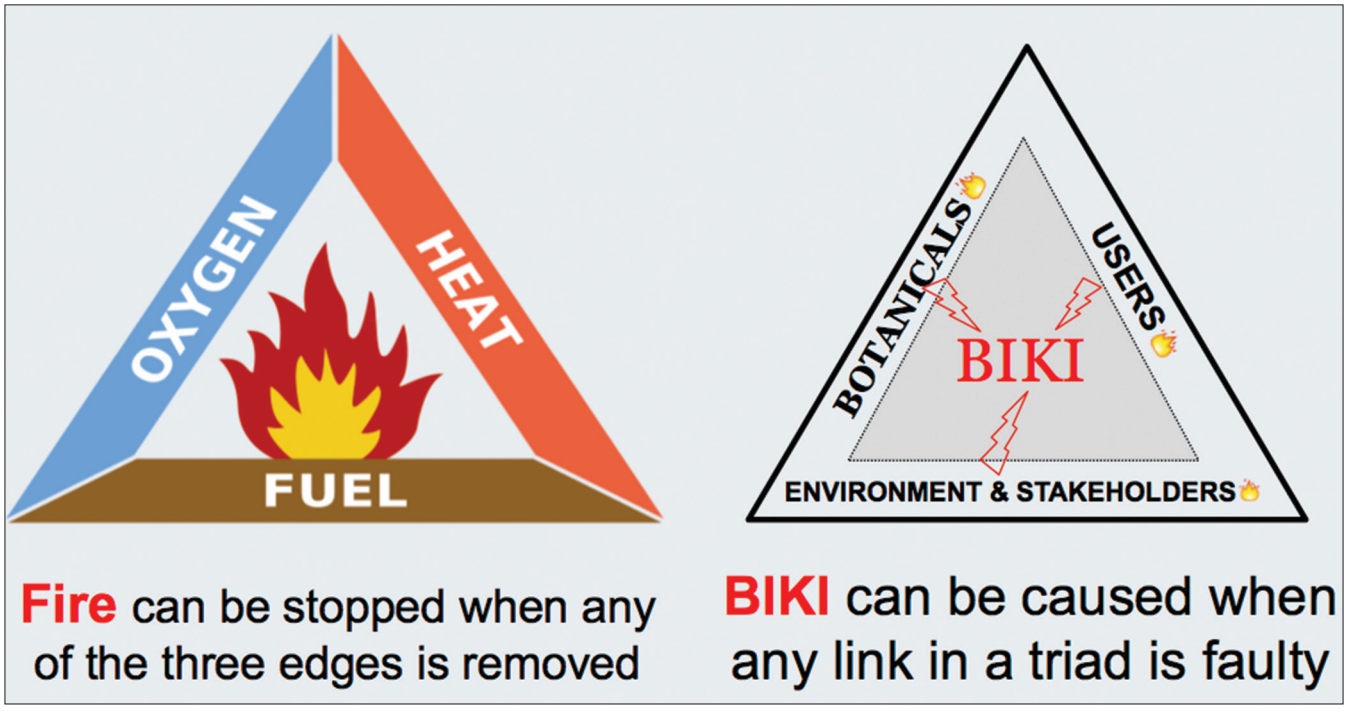

Figure 2: Botanical-induced kidney injury is trickier than fire and demands an integrated approach to prevention

triggered when any of the botanicals-users-stakeholders triads is faulty [Figure 2]. Thus, BIKI prevention demands a sophisticated approach integrating data on botanicals and usage, individualized response after exposure, as well as environment and stakeholders, including farmers, manufacturers, healthcare providers, and regulators, as proposed for herbal safety by Williamson *et al*.[25]

First, as having been emphasized by the FP7 GP-TCM consortium[123] and others,[124] the nomenclature issue is critical in developing integrative evidence, an integrative database, and an integrated approach to prevention. Adverse reaction reports, whether submitted to regulatory authorities or published in the literature, are meaningless and even misleading if the medicinal herb(s) or botanical ingredients in a product cannot be identified. Names for medicinal herbs include the Latin scientific name, the common or vernacular name, the pharmaceutical name or pharmacopeial name, or the specific herbal drug names (as those used in TCM). Herbal prescriptions, product packaging, or labels may have one or more of these depending on the source and regulatory status of the product. These have to be interpreted with care as even the scientific names may have synonyms. On this matter, Kew's Medicinal Plant Names Services (MPNS)[125] and the World Health Organization (WHO) Herbal Dictionary[126] can be expected to play a leading role. A botanically correct label does not necessarily confirm that the product contains what is listed on the label and that the concerned botanicals are not adulterated or contaminated and are in the expected quality and quantity. In cases of serious adverse reactions where specific toxins are suspected, laboratory analysis of the product/herb may be advisable to verify the reports. Beyond naming, labeling and prescription information, processing and preparation, administration route, dosing and timing are all important factors that may affect BIKI.

Second, in an era which aims for personalized medicine, individual factors including botanical user's age, sex, pregnancy status, diet, genetic background, educational status, health status, ability and willingness to understand and adhere, self-prescription, nutritional status, and health habits can all be important factors that affect BIKI. According to TCM theories, different patients with the same diseases or the same patient at the different stages of disease may vary in terms of TCM diagnosis. Many TCM practitioners believe that botanical prescription and use guided by TCM diagnosis may minimize risk-benefit ratio and this belief deserves further investigation. Third, environment has an important place in Good Agriculture and Collection Practice and Good Manufacture Practice and profoundly affects the quality of botanical materials and products. Thus, environment, through affecting quality of botanical materials and products, plays important roles in BIKI. Fourth, the roles for stakeholders ranging from vendors, healthcare providers, regulators, scientists, professional organizations, and their interaction with botanicals and botanical users can never be overemphasized.

Proactiveness is required

A reliable database that we have proposed above will help identify new cases of suspected BIKI. Meanwhile, we must identify and avoid exposure to risks proactively. Each phenotype and identified mechanisms of BIKI may be area of focused studies for better integrative evidence, better understanding of mechanisms, better tools for diagnosis, and better prevention.

First, current literature particularly focuses on the AKI phenotype based on markers such as serum creatinine or blood nitrogen urea. However, a rise in these markers occurs only after significant kidney injury,[127,128] suggesting the need for more sensitive and earlier detection. Serum creatinine also varies depending on age, gender, muscle mass, and nutrition,[129] reducing its reliability. Therefore, the development of new biomarkers may lead to better understanding, diagnosis of the AKI type of BIKI, ultimately leading to better care.

For instance, heme oxygenase-1 (HO-1), which is involved in heme degradation,[130] could be a potential biomarker for *in vitro* screening and early marker of BIKI. The function of HO-1 is not completely understood. Both *in vitro* and *in vivo* models of injury have suggested that endogenous HO-1 is cytoprotective, and chemical or genetic inhibition of HO-1 increases cell death and tissue necrosis.[130] This is further supported by studies of HO-1 knock-out mice, whereby targeted deletion of the enzyme leads to death in utero or within 1 year of birth.[131,132] Mice that survived beyond 1 year had many abnormalities such as growth retardation, anemia, iron deposition in the organs, and chronic inflammation such as glomerulonephritis, in addition to cells which were more susceptible to oxidative stress from endotoxins. HO-1 expression has been shown to be highly upregulated in response to cell injury mediated by oxidative or pro-inflammatory stress, heavy metals, ischemia, and hypoxia,[130] and renal HO-1 expression is increased in animal models of many types of AKI.[133-135] HO-1 was upregulated in the urine of patients with AKI or tubulointerstitial damage.[136] This suggested that HO-1 expression could be applied as a diagnostic tool to identify and monitor patients with kidney disease. A recent study aimed to identify a consistent biomarker of nephrotoxicity through gene expression profiling of human proximal tubular epithelial cells postexposure to different concentrations of nephrotoxicants.[137] The gene for HO-1 was significantly induced, in a dose-dependent fashion, by 6 out of 9 nephrotoxic compounds, including AAs, highlighting its potential as a biomarker.[137] As not all nephrotoxic compounds induce HO-1, the underlying mechanisms and other new biomarkers are surely needed.

As mentioned earlier, causal links between botanicals and CKD phenotype are difficult to establish clinically. In view that fibrosis is a cardinal feature of progressive CKD and that certain botanicals have been associated with epithelial-to-mesenchymal transition in epithelial cells and fibrogenesis in renal fibroblasts and in animal models,[138] it is likely *in vitro*, *in vivo*, and *in silico* models for detecting

botanical-induced epithelial-to-mesenchymal transition and fibrogenesis may be useful to identify botanicals that may cause CKD, leading to required labelling or banning from the marketplace. Similarly, botanical products could be screened for other phenotypes and mechanisms of BIKI in creative models. These will collectively contribute to the success of proactive and integrative pharmacovigilance for the prevention of BIKI.

Concluding Remarks

BIKI is an important and complex societal and medical problem. Learning from past lessons, we have proposed it as priorities to develop an authoritative BIKI database and to adopt a proactive, integrated approach to prevention. Building on existing expert opinions [e.g., those summarized in Table 1], we call for international leadership and interdisciplinary cooperation toward establishing a one-stop, open-access, user-friendly, high-quality, human-curated, and regularly updated BIKI database.

Despite all the challenges, we believe that harmonization of botanical pharmacovigilance with current pharmacovigilance system designed to report adverse drug reactions (ADR) induced by pure compounds is possible. We suggest that the WHO is uniquely qualified to play a leading role in this initiative. The international stature of WHO provides the legitimacy needed for such a global issue, and the most recent election of Dr. Tedros Adhanom Ghebreyesus as the first African Director-General of this global agency may be an opportunity. Traditional medicine plays a major role in achieving universal health coverage and should be made safer and more reliable. Funding for such a long-term project could come from the member states and other fundraising channels and could include funds that currently support the Traditional, Complementary, and Integrative Medicine program of the WHO and the US National Center for Complementary and Integrative Health, for example. The initiative should involve the WHO Collaborating Centre for International Drug Monitoring, Uppsala Monitoring Centre (UMC), MPNS, national and international medical, pharmacological, toxicological, and pharmacovigilance centers and societies, as well as individuals such as experts involved in the work listed in Table 1.

Illustrative is the work of UMC, which takes ADR reports from over 100 countries around the world. The UMC database contains millions of reports, including tens of thousands related to herbal or natural products. These reports are incorporated into a single database, with review of suspected signals carried out by experts in relevant fields.[23,139] Unfortunately, kidney-related ADR was rarely reported by UMC. This either means that kidney-related ADR is rare or more likely that nephrology practitioners are insufficiently aware of this resource.

National regulators also have an important role to play. Recently, FDA has launched a new adverse event portal that enables drug developers, doctors, and patients to search for safety red flags for approved drugs. This FDA Adverse Event Reporting System offers a powerful postmarketing pharmacovigilance resource and a means of guiding preclinical drug development.[140] This new portal can also serve as a potential platform for pharmacovigilance of nephrotoxic botanicals.

After all, as Theodore Roosevelt said: "Risk is like fire: if controlled it will help us; if uncontrolled it will rise up and destroy us." Botanicals are such risks. They can become valuable remedies or cause damage. It all depends on how well we know them and whether they are used appropriately.

Financial support and sponsorship

The authors would like to thank Kidney Research UK, Innovation China UK, European Union and the Intramural Research Program, NIDDK, NIH for funding of this important line of research.

Conflicts of interest

There are no conflicts of interest.

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Supplementary Table 1: Botanicals associated with the acute kidney injury phenotype of botanical-induced kidney injury

Botanical	Nephrotoxic manifestations	References and levels of evidence
Aristolochia spp.	AKI (ATN or AIN), CKD and tubular disorder	Epidemiological survey[1] Animal model[2] Case-control[3] Cohort study[4]
Callilepis laureola and other atractyloside-containing spp.	AKI (ATN)	Case report[5] Case report[6] Retrospective study[7]
Cupressus funebris, *Taxus celebica*, and other nephrotoxic flavonoids-containing spp.	AKI (AIN or ATN)	Case report[8] Case report[9]
Tripterygium wilfordii Hook F	AKI (ATN)	Animal model[10] Animal model[11] Case report[12] Animal model[13] Animal model[14]
Aloe spp.	AKI (AIN)	Case report[15] Animal model[16]
Teucrium polium	AKI (ATN)	Animal model[17]
Artemisia absinthium (wormwood)	AKI	Case report[18]
Uncaria tomentosa or *Uncaria guianensis* (cat's claw)	AKI (AIN)	Case report[19]

AKI: Acute kidney injury, ATN: Acute tubular necrosis, AIN: Acute interstitial nephritis, CKD: Chronic kidney disease

Supplementary Table 2: Botanicals associated with the nephrolithiasis phenotype of botanical-induced kidney injury

Botanical	Nephrotoxic manifestations	Reference and levels of evidence
Vaccinium spp. (Cranberry)	Nephrolithiasis	RCT[20] Cohort study[21]
Rheum officinale (Rhubarb)	Nephrolithiasis (may lead to AKI)	Case report[22]
Averrhoa carambola (Star fruit)	Nephrolithiasis (may lead to AKI)	Case report[23] Animal model[24] Animal model[25] Case report[26] *In vitro* evidence[27] *In vitro* evidence[28]
Herniaria hirsuta L. (Hairy Rupture Wort)	Nephrolithiasis	Animal model[29] *In vitro* evidence[30] Animal model[31]
Ephedra sinica *Guaiacum officinale*	Nephrolithiasis	Case report[32] Systematic review[33] Case report[34] Case report[35] Case report[36] Cohort study[37] Case report[38]

RCT: Randomized controlled trial, AKI: Acute kidney injury

Supplementary Table 3: Botanicals associated with the tubular dysfunction phenotype of botanical-induced kidney injury

Botanical	Nephrotoxic manifestations	References and levels of evidence
Aristolochia spp.	Tubular dysfunction, which can manifest as Fanconi syndrome	Animal model[39] Cohort study[40] Case report[41] Case report[42]
Juniperus communis (Juniper berries)	Tubular dysfunction, which can manifest as diuresis, etc.	Animal model[43]
Fucus vesiculosus (Bladderwrack)	Tubular dysfunction, characterized by degeneration	Case report[44]
Cleistanthus collinus	Tubular dysfunction, characterized by distal renal tubular acidosis	Cohort study[45] Animal model[46] Case report[47] Case report[48]

Supplementary Table 4: A summary of proposed mechanisms of botanical-induced kidney injury

Mechanism of nephrotoxicity	Plant species	Nephrotoxic manifestation and pathogenesis	Reference and level of evidence
Inducing cell death	*Aristolochia* spp.	AKI: Inducing apoptosis and interfering with cell cycle in tubular cells	*In vitro*[49] *In vitro*[50] Animal model[51] *In vitro*[52]
	Averrhoa carambola (star fruit)	AKI: Focal tubular deposition of crystals inducing apoptosis with fragmentation and cytoplasmic vacuolization	*In vitro*[24] *In vitro*[25] *In vitro*[27] *In vitro*[28]
	Atractyloside-containing spp.	AKI: Inhibition of mitochondrial ATP synthesis; mitochondrial membrane permeability pore activation	Animal model[53] *In vitro*[54] Animal model[55] Animal model[56]
	Tripterygium wilfordii	AKI: Inducing oxidative stress, reducing superoxide dismutase and glutathione peroxidase	Animal model[14]
	Cleistanthus collinus	AKI and tubular dysfunction: Inhibition of cell division and DNA synthesis; reduction of glutathione and ATPases, leading to oxidative stress	*In vitro*[57] *In vitro*[58] *In vitro*[59] *In vitro*[60] *In vitro*[61]
	Aconitum spp., e.g., *Aconitum carmichaelii or Allium tanguticum*	AKI: Inhibiting the tricarboxylic acid cycle in myocardium, leading to renal ischemia and hypoxia, releasing oxidative stressors which activate proapoptotic genes in renal cells	Animal model[62]
Blockade of renal transport processes	*Harpagophytum procumbens* (Devil's claw)	AKI: Downregulates P-glycoprotein transporter expression and activity	*In vitro*[63]
	Tripterygium wilfordii Hook	Tubular dysfunction: Inhibits specific segments of organic anion transporters, required for secretion and absorption	Animal model[64]
Crystal and stone formation	*Vaccinium* spp. (cranberry)	Nephrolithiasis: Contains high concentrations of oxalate	RCT[20] Cohort study[21]
	Averrhoa carambola (star fruit) and *Rheum officinale* (rhubarb)	Nephrolithiasis and AKI: Focal tubular deposition of calcium oxalate crystals due to high oxalic acid content	Case report[22] Case report[23] Animal model[24] Animal model[25] Case report[26] *In vitro*[27] *In vitro*[28] Literature review[65]

Contd...

Supplementary Table 4: Contd...

Mechanism of nephrotoxicity	Plant species	Nephrotoxic manifestation and pathogenesis	Reference and level of evidence
	Ephedra sinica; Guaiacum officinale	Nephrolithiasis: Poor solubility leads to precipitation out of the urine when consumed in large quantities	Case report[32] Systematic review[33] Case report[34] Case report[35] Case report[36] Cohort study[37] Case report[38] Case report[66]
Carcinogenesis	*Aristolochia* spp.	UUC/RCC: AA-derived ions form covalent adducts with DNA purine bases, causing TP53 mutation	Molecular and epidemiological evidence[67-71]
Hypertension	*Glycyrrhiza glabra*	CKD: Inhibition of renal 11ß-hydroxysteroid dehydrogenase, leading to inappropriate activation of mineralocorticoid receptors	Case report[72] Animal model[73] *In vitro*[74] Clinical study[75] Animal model[76] Animal model[77]
	Ephedra spp.	CKD: Sympathomimetic activity	Case report[78] RCT[79]
Idiosyncratic	*Uncaria tomentosa*	AKI: Type B IgE-mediated allergic reaction	Case report[19]

AKI: Acute kidney injury, UUC: Upper urinary tract urothelial cancer, RCC: Renal cell carcinoma, CKD: Chronic kidney disease, IgE: Immunoglobulin E, AA: Aristolochic acid, RCT: Randomized controlled trial, ATP: Adenosine triphosphate

References to Supplementary Tables

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