

REVIEW

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Overview on pharmacovigilance of nephrotoxic herbal medicines used worldwide

Noufissa Touiti^{1,2*}, Tarik Sqalli Houssaini³ and Sanae Achour^{1,4,5}

Introduction

There is a growing use of herbal medicines worldwide. Especially in patients with chronic diseases such as kidney disease, when numerous studies have shown a generalized high prevalence [1–4]. However, there are concerns about herbal medicines and their ability to produce harmful effects. Examples from the literature have clearly shown the association between the use of herbs and kidney disease [5, 6]. The increasing use of herbal medicines has increased the need to monitor their safety. Thus, the approach recommended by the World Health Organization (WHO) was to include herbal medicines in existing national pharmacovigilance systems [5]. The pharmacovigilance of medicinal plants or phytovigilance involved the evaluation of the risks and benefits of phytotherapy. The ultimate goal is to protect patients from herbal harm [6]. It is essential to develop reliable information on the safety of herbal medicines [7]. Becoming necessary due to risks of toxicity (acute or chronic) or risks of drug interactions (of pharmacokinetic or pharmacodynamic nature), as regards interactions between several associated plants, phytovigilance also represents a legal obligation [8]. Several issues related to how herbal medicines are named, perceived, obtained and used [9]. At international level, the WHO published guidelines on pharmacovigilance of herbal medicines [10]. However it is still a new activity in the majority of countries of Africa. Except in Morocco where a pharmacovigilance program in phytotherapy was created in 2000 [6]. Also the creation of Botanicus and Phytotox

[11]. This situation requires knowledge, recognition and monitoring of adverse reactions through pharmacovigilance of herbal medicines activities [12, 13]. In order to show renal sides effects of herbal medicines use and current need to monitor phytovigilance worldwide, systematic research was carried out on PubMed, Science direct and Scopus. Moreover, some accessible databases on pharmacovigilance of herbal medicine or phytovigilance were consulted (Table 1). The aim of this article was to provide an overview of nephrotoxicity associated with the use of herbal medicines.

Materials and methods

Search strategy

Electronic literature searches were conducted in Mai 2020 to identify case reports of nephrotoxicity associated with herbal medicines use in the last two decade. The scientific resources including PubMed, Scopus, and Science direct were searched using key words such as: 'case report', 'Renal side effect', 'adverse effects', 'Nephrotoxicity', 'Risk', 'Herbal Medicine', 'kidney disease'. The spectrum of herbal induced kidney injuries included kidney stones, nephritis, nephrotic syndrome, necrosis, acute kidney injury, chronic kidney disease, and death. English articles were the primary focus, but some reports in other languages were considered.

Inclusion and exclusion criteria

Eligible studies had to fulfil the following criteria: Included studies were case reports of nephrotoxicity associated to herbs use worldwide between 2000 and 2020.

Exclusion criteria: Case reports were excluded if they involved mushrooms, poisonous plants, self-harm, excessive doses (except vitamins/minerals), drug-herbal interactions and commercial dietary supplement.

* Correspondence: noufissa.touiti@usmba.ac.ma

¹Laboratory of Biomedical and Translational Research, Faculty of Medicine and Pharmacy of Fez, Sidi Mohammed Ben Abdellah University, Fez, Morocco

²Faculty of Science and Technology of Fes, Sidi Mohammed Ben Abdellah University, Fez, Morocco

Full list of author information is available at the end of the article

Table 1 Case reports included

Herb	Country	Gender	Age (years)	Reason	Preparation	Renal side effect	Causality	Reference
<i>Dioscorea quinqueloba</i>	Korea	male	52	cardiovascular disease	Raw extract	biopsy-proven acute interstitial nephritis	Certain	2014, [14]
<i>Dioscorea quinqueloba</i>	Korea	male	51	for his own health	dug up tubers of <i>D. quinqueloba</i> and drank about 400 mL of juice made from the raw tubers	acute kidney injury	Probable	2015, [15]
<i>Dioscorea quinqueloba</i>	Korea	male	68–58	Diabetes mellitus and health tonics	extract from tubers	acute kidney injury	Possible	2011, [16]
<i>Cape aloes</i>	Soweto, South Africa	male	47	to clean his stomach	Taken the remedy by mouth at least three times during the month before admission, with the last dose about 10 days before admission.	acute oliguric renal failure and liver dysfunction	Certain	2002, [17]
<i>Glycyrrhiza glabra</i>	Serbia	female	39	sterility	ingestion of 50–100 g herbal products which contained licorice, every day for 8 weeks	Acute Renal Failure	Probable	2010, [18]
Unknown herbal vaginal pessary	Nigeria	female	22	To terminate an unwanted pregnancy	insertion of a locally prepared herb (semi-solid) into her genital tract	oliguric acute kidney injury	Probable	2017, [19]
<i>Chenopodium polyspermum</i>	Anatolia region, Turkey	male	45	to regulate his blood glucose levels		chronic renal failure	Possible	2012, [20]
<i>Nigella sativa</i>	Turkey	female	62	antioxidant or antidiabetic effects	<i>N. sativa</i> tablets for 6 d at approximately 2000 to 2500 mg/d.	acute renal failure	Possible	2013, [21]
<i>Tribulus terrestris</i> <i>Avena sativa</i> <i>Panax ginseng</i> <i>Zingiber officinale</i>	Turkey	female	50	cardio-protective	4 different combination herbal medicinal products twice a day for 2 weeks	Acute kidney injury	Possible	2014, [22]
<i>African mango (Irvingia gabonensis)</i>	Turkey	female	42	slimming purposes	Three months previously she started using 2 × 500 mg African mango	rapid renal progression	Probable	2015, [23]
<i>Lawsonia inermis</i>	Myanmar	male	34	swelling of his face and unhealthy appearance of his skin.	boiled henna leaves, of which he drank about 700 mL/ day for 3 days	acute kidney injury	Probable	2017, [24]
<i>Lawsonia inermis</i> L.	Kingdom of Saudi Arabia	male	32	chronic bloating and constipation	ingestion of large amounts of boiled henna	acute renal failure	Probable	2013, [25]
<i>Artemisia herba-alba</i>	Tunisia (North Africa)	male	59	antidiabetic agent	aqueous extract (two cups a day for two consecutive days)	acute tubular necrosis	Possible	2010, [26]
<i>Euphorbia paralias</i>	Tunisia	male	29	edema	one time ingestion of boiled plant of <i>Euphorbia paralias</i> ten days before	acute renal failure	Possible	2013, [27]
<i>Cassia senna</i> L.	Belgium	female	52	constipation	had ingested, for > 3 years, one liter of an herbal tea each day made from a bag containing 70 g of dry senna fruits	acute hepatic failure and renal impairment	Possible	2005, [28]
ayurvedic powder	India	male	33	eczematous skin lesions	Ingestion of ayurvedic contained arsenic for last 6 months	acute kidney injury	Possible	2011, [29]
ayurvedic	India	female	44	to reduce the	Contained high levels of	acute renal failure	Possible	2015, [30]

Table 1 Case reports included (*Continued*)

Herb	Country	Gender	Age (years)	Reason	Preparation	Renal side effect	Causality	Reference
medication				side effects of chemotherapy	several heavy metals including those of mercury, lead, and manganese			
ayurvedic supplement	India	male	24	fever and abdominal pain	Ingestion of Alternative Medicine Containing Lead	acute kidney injury	Possible	2019, [31]
<i>Carica papaya</i>	India	male	62	increase the platelet count	juice extracted from papaya leaves	acute kidney injury	Possible	2019, [32]
<i>Tribulus terrestris</i>	Iran	male	28	to prevent kidney stone formation	2 L of <i>T. terrestris</i> water in two consecutive days	nephrotoxicity	Probable	2010, [33]
<i>Aristolochia manshuriensis</i>	chine	male	41	urinary tract infection	4 boxes (each containing 40 small packets) of an herbal preparation called "Fen Qing Wu Lin Wan". That was taken twice daily for twenty consecutive days.	died in renal failure	Certain	2010, [34]
<i>Trigonella foenum-graecum</i>	Iran	female	62		daily ingestion of heat extract of fenugreek	acute interstitial nephritis	Possible	2017, [35]
<i>Crataegus orientalis</i>	Turkey	male	68		eating ½ kg of raw and drinking five cups of tea made from leaves 3 days before	Acute renal failure	Possible	2008, [36]
<i>Tripterygium wilfordii</i> Hookf	Southwest china	male	36.6		ingesting approximately 50 g of wild honey	3 patients were at different degrees of renal damage, and 1 patient with severe symptoms died of acute renal failure 1 day after admission	Not excluded	2016, [37]
<i>Colchicum autumnale</i>	Croatia	male	62		ate a salad of plant with green leaves regarded as wild garlic	nephrotoxic acute tubular necrosis	Possible	2004, [38]
<i>Rheum rhaponticum</i>	Germany	female	52		increased ingestion of approximately 500 mg of rhubarb (fresh weight) per day in the last 4 weeks	acute renal failure	Possible	2012, [39]
<i>Pithecellobium jeringa</i>	Malaysia	male	45			acute renal failure	Not excluded	2007, [40]

Study selection and data extraction

Studies titles retrieved by the search were assessed for inclusion by one reviewer and a sample of excluded titles was checked by a second reviewer: no instances of discrepancy were found. Potentially relevant abstracts and full texts were assessed by two reviewers and any discrepancies resolved through discussion. Data were extracted by one reviewer and checked by a second. The causality was assessed by using Naranjo causality assessment scale [12], adapted as described in our recent publication [13].

Results

Description of studies included

The comprehensive search retrieved over 15,303 citations and 47 of them were examined in full text (Fig. 1). Eighty-five percent of the studies were excluded. As a

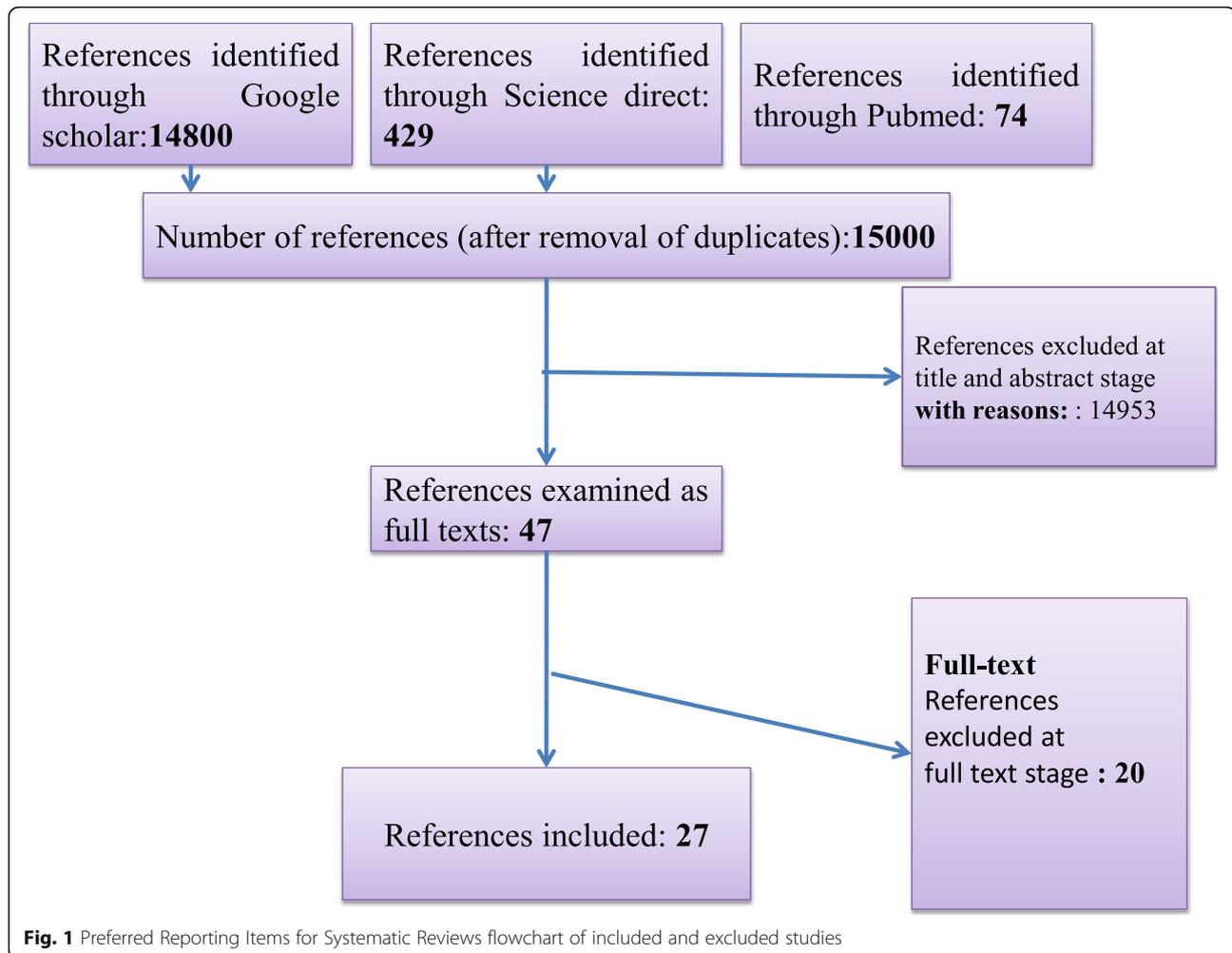
result, 27 eligible studies were included. The key data from these reports are summarized in Table 1.

Adverse effects of herbal medicines and need of phythovigilance

Case reports of renal side effects associated to herbs usage worldwide

In our search, twenty seven case reports of nephrotoxicity related to the consumption of herbs were identified around the world from Southeast Asia, Korea, South and North Africa, Turkey, Tunisia and from Belgium. The renal reactions involved mostly males (18/27 = 66%), between 22 and 68 years old. The characteristics of cases are reported in Table 1.

Various renal syndromes were reported after the use of medicinal plants, including acute tubular necrosis,



acute interstitial nephritis, acute kidney injury, and chronic renal failure.

Reports of nephrotoxicity associated with herbal medicines use encompass all forms of renal dysfunction, ranging from acute to chronic renal failure and death.

The herbal medicines most commonly associated with nephrotoxicity were: *Dioscorea quinqueloba*, *Lawsonia inermis*, *Cassia senna L.*, *Artemisia herba-alba*, *Chenopodium polyspermum*, *Cape aloes*, *Euphorbia paralias*, *Crataegus orientalis*, *Colchicum autumnale* and *Tribulus terrestris*.

The causality assessment between consumption of herbal preparation and renal reaction, carried out according to Narranjo method, resulted as certain in four cases, probable in seven cases and as possible in fifteen cases. Other details on adverse reactions are described in Table 1.

Why is Phytovigilance of nephrotoxic herbal medicines important in nephrology?

A phytovigilance system needs to be established in order to assess renal adverse effects caused by herbal

medicines. Many recommendations were published to dress this issue; some of them are summarized in Table 2.

Discussion

The use of traditional herbal medicine is common worldwide. Indeed, up to 80% of the population relied on herbal concoctions for their primary health care [4], [54]. Herbal products are preferred because they are natural. In addition, they are considered “safe” and “have fewer side effects” than “synthetic drugs”. On the other hand, plants contain a number of active ingredients that produce a physiological effect in the body [55]. This overview aimed to highlight nephrotoxicity of herbal medicines use in the last two decade. Even rare, reported cases of kidney side effects associated with the use of herbal medicines were very serious worldwide. Indeed we noted twenty seven case reports of nephrotoxicity related to herbal medicines. Another review found that 44 reported cases of nephrotoxicity were associated with

Table 2 Reviews recommendations on pharmacovigilance of nephrotoxic herbal medicines

Recommendations	Reference
medicinal plants are associated with the pathogenesis of renal diseases in order to update healthcare practitioners to keep abreast with the current information on the medicinal herbal therapies and consequences that may be associated with such health-seeking behaviors	[41]
Some evidence was in line with the potential nephrotoxicity of plants and their reformers. Despite the lack of clinical research for evaluation of their renal damage, the herbs may be focused in term of their nephrotoxicity; and there is a need for further studies on the scientific basis of their nephrotoxicity	[42]
Strict controls on the presence of adulterants within herbal medicines, labeling of dosages and contraindications, and manufacturing techniques must be maintained to ensure the safety of those consuming herbal medicines.	[43]
Clinicians should consider herbal medicine use in patients with unexplained acute kidney injury or progressive chronic kidney disease. In addition, exposure to herbal medicine containing aristolochic acid may increase risk for future uroepithelial cancers, and patients require appropriate postexposure screening	[44]
it is important that alternative medicines not be demonized as a whole, but that their use and consequences be closely observed and reported to build a more comprehensive understanding of their impact in our clinical practice and to foster research on the potential harm or, in some cases, possible benefits	[45]
Considering the complexity of the toxic components and the diversity of their acting pathway, a lot of work needs to do on pharmacovigilance, "Omics" technologies, and administration of mixtures alleviating toxicities. Pharmacovigilance methods can be used for monitoring kidney toxicity traditional Chinese medicines safety. "Omics" technologies have the potential for the development of molecular markers hopefully allowing for detection of early changes in toxic kidney injury with high sensitivity and specificity. These researches may help us to deeply learn the mechanism of traditional Chinese medicines renal toxicity at the molecular and gene level	[46]
Use of modern cell biological, biochemical, in vitro and in vivo techniques for the evaluation of medicinal plants safety is needed	[47]
Herbal medicines related to either severe or moderate adverse events supported by a case report should be avoided.	[48]
Cooperation between orthodox physicians and traditional practitioners is needed to bring together the full case details. Independent scientific assistance on toxicological investigation, botanical verification can be invaluable for full evaluation of any case report. Systematic pharmacovigilance is essential to build up reliable information on the safety of herbal medicines for the development of appropriate guidelines for safe effective use	[7]
It is deemed necessary that a basic knowledge of the pharmacological aspects of phytotherapy be included in the regular Course of Medicine.	[49]
<i>Phytovigilance: A medical requirement and a legal obligation</i>	[8]
<i>Need to incorporate pharmacovigilance of herbal medicine to the curriculum</i>	[50]
There is a need for herbal medicine regulation, technical and training assistance, and funding as being major challenges to HM pharmacovigilance in countries. Particular attention to the development of pharmacovigilance of herbal medicine is required in Africa.	[6]
The use of indigenous drugs, herbal medicine and traditional <i>materia medica</i> can only be understood through a combination of historical, ecological, economic, cognitive, and pharmacological approaches, while anecdotal references are lost in space and time.	[51]
A demonstration of the safety of herbal medicines for registration purposes should include at least in vitro and in vivo genotoxicity assays, long-term rodent carcinogenicity tests (for drugs intended to be continuously used for > 3 months or intermittently for > 6 months), reproductive and developmental toxicity studies (for drugs used by women of childbearing age), and investigation of the effects on drug-metabolizing enzymes.	[52]
Government organizations should assume responsibility to provide active guidance and effective regulation	[53]

herbal or dietary supplements worldwide [48]. Nephrotoxic herbs most reported were:

Lawsonia inermis

Henna is a traditional cosmetic agent and is used worldwide, not only as a cosmetic agent but also is applied to the body on lesions in the treatment of seborrheic dermatitis or fungal infections. Different pathologies have been described as caused by henna. For this reason people should be informed about the side-effects of topical henna application and clinicians should be aware of these manifestations [56]. Lawsone (2-hydroxy-1,4 naphthoquinone) is a chemical agent present in henna [4–6]. It has been shown to cause severe haemolytic anaemia and renal tubular necrosis in animals [56]. Most reports of henna toxicity have been attributed to adding

a synthetic dye para-phenylenediamine (PPD). Indeed unreliable quality can be a problem. In particular, this poses a risk when herbal medicines are contaminated (e.g. with heavy metals) or adulterated (e.g. with prescription drugs) [57]. Another example for herbs contamination nephrotoxicity was ayurvedic supplement from India, which contained high levels of several heavy metals including those of mercury, lead, arsenic and manganese. In fact, previous overview reported that herbal medicinal products were adulterated or contaminated with dust, pollens, insects, rodents, parasites, microbes, fungi, mould, toxins, pesticides, toxic heavy metals and/or prescription drugs. The most severe adverse effects caused by these adulterations were agranulocytosis, meningitis, multi-organ failure, perinatal stroke, arsenic, lead or mercury poisoning, malignancies

or carcinomas, hepatic encephalopathy, hepatorenal syndrome, nephrotoxicity, rhabdomyolysis, metabolic acidosis, renal or liver failure, cerebral edema, coma, intracerebral haemorrhage, and death. Adulteration and contamination of herbal medicinal products were most commonly noted for traditional Indian and Chinese remedies, respectively [58].

Cassia acutifolia and *angustifolia* plants are widely used as laxatives. The mechanism of renal injury remains debatable. Massive loss of fluid and electrolytes during laxative abuse may cause renal dysfunction. Moreover, a direct cytotoxic effect on the tubular cells may also be involved, as it has been shown that anthraquinone derivatives may be accumulated in the kidneys [59], [60].

Crataegus spp. (hawthorn) monopreparations are predominantly used for treating congestive heart failure. Data from the literature indicated that hawthorn is rarely associated with serious adverse events. However, the unsupervised use of this drug can be associated with problems, especially if given with concomitant medications [61].

Artemisia herba-alba, *Artemisia herba-alba* Asso (Asteraceae) essential oil contained in majority: cis-chrysanthenyl acetate (25.12%); (2E,3Z) 3,5-heptadienal-2-ethyliden-6-methyl (8.39%); α -thujone (7.85%); myrtenyl acetate (7.39%); verbenone (7.19%), chrysanthenone (4.98%) [62].

Cape aloes

The Aloe plant is employed as a dietary supplement in a variety of foods and as an ingredient in cosmetic products. The widespread human exposure and its potential toxic and carcinogenic activities raise safety concerns. Chemical analysis revealed that the Aloe plant contained various polysaccharides and phenolic chemicals, notably anthraquinones [63]. Ingestion of Aloe preparations is associated with diarrhea, hypokalemia, pseudomelanosis coli, kidney failure, as well as phototoxicity and hypersensitive reactions [63].

Dioscorea quinqueloba

belonging to the family Dioscoreaceae, the most important identified compound from *Dioscorea* species is diosgenin [64].

From the most reported renal adverse effect we noted acute interstitial nephritis and acute kidney injury; which is similar with other study [13].

Tripterygium wilfordii's nephrotoxic power is well known. According to a recent systematic review and meta-analysis on its nephrotoxicity, the incidence rate of nephrotoxicity in *Tripterygium wilfordii* Hook. f preparations was 5.81% [65]. A single case report of *Tripterygium wilfordii* hook f's renal and cardiac toxicity in a

36-yr-old man has been reported. Three days after ingesting thunder god vine extract, the patient presented with profuse nausea, vomiting, diarrhea, leukopenia, renal failure, hypotension, and extensive cardiac abnormalities. The patient died 3 d after presentation from intractable shock. The authors could not differentiate the cause of this patient's renal dysfunction, postulating that it could have been supplement-induced nephrotoxicity, in conjunction with prolonged shock [66].

Colchicum autumnale is an herbaceous plant in the liliaceae family. Accidental poisonings by this plant generally result from a botanical confusion, with other edible herbaceous liliaceae; wild leek (*Allium polyanthum*) or wild garlic (*Allium ursinum*). This confirms that a simple confusion when identifying a plant deemed edible can have particularly deleterious consequences for patients [67].

Aristolochia manshuriensis

Chinese herbal medicine has been practiced for the prevention, treatment, and cure of diseases for thousands of years. Some of the nephrotoxic components from herbs are aristolochic acids and other plant alkaloids [44]. A recent review has listed case reports of nephrotoxicity due to Chinese herb species containing aristolochic acid [68]. The kidney manifestations of nephrotoxicity associated with Chinese herbal medicine included acute kidney injury, CKD, nephrolithiasis, rhabdomyolysis, Fanconi syndrome, and urothelial carcinoma [44].

Glycyrrhiza glabra (licorice) Natural licorice is extracted from *Glycyrrhiza glabra* root containing glycyrrhizin or glycyrrhizic acid in sufficient quantities it affects blood pressure and causes other health issues. Licorice has been involved in the renal disease by inhibiting major renal transport processes needed for filtration, secretion, and absorption [69]. Hence, licorice should be carefully monitored for its use in patients with renal problems [70].

However, we observed the absence of some much known nephrotoxic plants in the two last decade, it is notably Ephedra species [71], *Tripterygium wilfordii* hook f [66]. What shows some phytovigilance that needs to be more increased.

Several reviews have listed a list of nephrotoxic plants and have proposed several recommendations concerning the fight against this use [72], [70]. Which shows the interest of creating a pharmacovigilance system for these plants particularly for nephrology.

The potential of natural products to cause renal dysfunction is justifiable. It is imperative that the use of natural products be closely monitored in all patients. Healthcare professionals should take an active role in identifying patients using natural products and providing

appropriate patient education [72]. Indeed we summarized some published recommendations in this way.

Herbal medicine uses medicinal plants prepared by means of adapted extracting technologies and appropriate pharmacological preparations, purified and standardized in their chemical principles. As with any form of therapy, there are possible side effects, contraindications, pharmacological interactions. It is considered necessary that a basic knowledge of the pharmacological aspects of herbal medicine be included in the regular course of medicine [49]. Plant extracts can have kidney toxicity due to their inherent properties. If they exhibit some degree of toxicity, the risks can be weighed against the benefits and decisions can be made regarding their continued availability, in a manner similar to that currently done for nephrotoxic pharmaceutical agents. Importantly, the inherent properties of the herb are not the only source of kidney problems associated with plants, as plant-drug interactions, errors in dosing and identification, and contaminants in the mixture are all of concern. Strict controls on the presence of adulterants in herbal medicines, labeling of dosages and contraindications and manufacturing techniques must be maintained to ensure the safety of consumers of medicinal plants [73].

Conclusion

Herbal medicine seemed to present a real risk for the kidney. Case reports from the literature have clearly shown the association between the use of herbs and the occurrence of nephrotoxicity worldwide. Hence the need to incorporate a phytovigilance system in the nephrology service, especially in Africa and Asia.

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Ethics approval and consent

Not applicable.

Authors' contributions

Noufissa Touiti, Sanae Achour and Tarik Sqalli Houssaini analyzed Studies titles for inclusion and contributed in the writing of the manuscript. Noufissa Touiti, supervising the whole work. All authors read and approved the final manuscript.

Availability of data and materials

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Author details

¹Laboratory of Biomedical and Translational Research, Faculty of Medicine and Pharmacy of Fez, Sidi Mohammed Ben Abdellah University, Fez, Morocco. ²Faculty of Science and Technology of Fes, Sidi Mohammed Ben Abdellah University, Fez, Morocco. ³Research Team Kidney Laboratory of Molecular Bases in Human Pathology and Therapeutic Tools, University Hospital Center Hassan II, Fez, Morocco. ⁴Laboratory of Toxicology, University Hospital Center Hassan II, Fez, Morocco. ⁵Faculty of Medicine and Pharmacy of Fez, Fez, Morocco.

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