Overview on pharmacovigilance of nephrotoxic herbal medicines used worldwide

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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

Materials and methods
Search strategy
Electronic literature searches were conducted in May 2020 to identify case reports of nephrotoxicity associated with herbal medicines use in the last two decades. 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 fulfill 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.
| Herb             | Country                          | Gender | Age (years) | Reason                      | Preparation                                                                 | Renal side effect                                           | Causality       | Reference |
|------------------|----------------------------------|--------|-------------|-----------------------------|-----------------------------------------------------------------------------|-------------------------------------------------------------|-----------------|-----------|
| **Dioscorea**     | Korea                            | male   | 52          | cardiovascular disease      | Raw extract                                                                | biopsy-proven acute interstitial nephritis                  | Certain         | 2014, [14]|
| quinqueloba       |                                  |        |             |                              | dioscorea quinqueloba dug up tubers of D. quinqueloba and drank about 400 mL of juice made from the raw tubers | acute kidney injury                                        | Probable        | 2015, [15]|
| **Dioscorea**     | Korea                            | male   | 51          | for his own health          | Raw extract biopsy-proven acute interstitial nephritis                       | certain                                                    | 2011, [16]      |
| quinqueloba       |                                  |        |             |                              | extract from tubers                                                        | acute kidney injury                                        | Probable        | 2011, [16]|
| **Cape aloe**     | Soweto, South Africa             | male   | 47          | to clean his stomach        | Taken the remedy by mouth taken at least three times during the month before admission, with the last dose about 10 days before admission | acute kidney injury                                        | Certain         | 2002, [17]|
| **Glycyrrhiza**   | 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]|
| glabra            |                                  |        |             |                              |                                                                             | oliguric acute kidney injury                                | Probable        | 2017, [19]|
| **Unknown**       | Nigeria                          | female | 22          | To terminate an unwanted pregnancy | insertion of a locally prepared herb (semi-solid) into her genital tract    | chronic renal failure                                       | Possible        | 2012, [20]|
| herbal vaginal    |                                  |        |             |                              |                                                                             | acute renal failure                                        | Possible        | 2013, [21]|
| pessary           |                                  |        |             |                              |                                                                             | chronic renal failure                                       | Possible        | 2012, [20]|
| **Chenopodium**   | Anatolia region, Turkey          | male   | 45          | to regulate his blood glucose levels | N. sativa tablets for 6 d at approximately 2000 to 2500 mg/d.              | acute renal failure                                        | Possible        | 2013, [21]|
| polyspermum       |                                  |        |             |                              |                                                                             |                                                             |                 |           |
| **Nigella sativa**| Turkey                           | female | 62          | antioxidant or antidiabetic effects | 4 different combination herbal medicinal products twice a day for 2 weeks   | Acute kidney injury                                        | Possible        | 2014, [22]|
| **Tribulus**      | Turkey                           | female | 50          | cardio-protective           | 4 different combination herbal medicinal products twice a day for 2 weeks   | Acute kidney injury                                        | Possible        | 2014, [22]|
| terrestris        |                                  |        |             |                              |                                                                             |                                                             |                 |           |
| Avena sativa      |                                  |        |             |                              |                                                                             |                                                             |                 |           |
| **African mango** | Turkey                           | female | 42          | slimming purposes           | Three months previously she started using 2 x 500 mg african mango          | rapid renal progression                                     | Probable        | 2015, [23]|
| (Irvingia gabonensis) |                                    |        |             |                              |                                                                             |                                                             |                 |           |
| **Lawsonia**      | 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]|
| inermis           |                                  |        |             |                              |                                                                             |                                                             |                 |           |
| **Lawsonia**      | Kingdom of Saudi Arabia          | male   | 32          | chronic bloating and constipation | ingestion of large amounts of boiled henna                                  | acute renal failure                                        | Probable        | 2013, [25]|
| inermis L.        |                                  |        |             |                              |                                                                             |                                                             |                 |           |
| **Artemisia**     | Tunisia                          | male   | 59          | antidiabetic agent          | aqueous extract (two cups a day for two consecutive days)                   | acute renal failure                                        | Possible        | 2010, [26]|
| herba-alba        | (North Africa)                   |        |             |                              |                                                                             |                                                             |                 |           |
| **Euphorbia**     | Tunisia                          | male   | 29          | edema                       | one time ingestion of boiled plant of *Euphorbia paralias* ten days before   | acute renal failure                                        | Possible        | 2013, [27]|
| paralias          |                                  |        |             |                              |                                                                             |                                                             |                 |           |
| **Cassia senna 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**     | India                            | male   | 33          | eczematous skin lesions     | Ingestion of ayurvedic contained arsenic for last 6 months                   | acute kidney injury                                        | Possible        | 2011, [29]|
| powder            |                                  |        |             |                              |                                                                             |                                                             |                 |           |
| **ayurvedic**     | India                            | female | 44          | to reduce the              | Contained high levels of                                                   | acute renal failure                                        | Possible        | 2015, [30]|
| powder            |                                  |        |             |                              |                                                                             |                                                             |                 |           |
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 phytovigilance

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 primarily 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
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-chrysanthanyl acetate (25.12%); (2E,3Z) 3,5-heptadienal-2-ethyliden-6-methyl (8.39%); α-thujone (7.85%); myrtle acetate (7.39%); verbene (7.19%), chrysanthene (4.98%) [62].

**Cape ales**
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].

**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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Authors’ contributions
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Availability of data and materials
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Competing interests
The authors declare that they have no competing interests.

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References

1. Touiti N, Sqalli T, Iken I, Benslimane A, Achour S. Prevalence of herbal medicine use among patients with kidney disease : a cross-sectional study from Morocco. Néphéologie & Thérapeutique. 2020;16(1):43–9.
2. Kara B. Herbal product use in a sample of Turkish patients undergoing haemodialysis. J Clin Nurs. 2009;18:2197–205.
3. Lai M-N, Lai J-N, Chen P-C, Hsièh S-C, Hu F-C, Wang J-D. Risks of kidney failure associated with consumption of herbal products containing mu Tong or Fangchi: a population-based case-control study. Am J Kidney Dis. 2010;55(3):507–18.
4. Corinne Isnard Bagnis, MD, PhD, Gilbert Deray, Alain Baumeolou , MD, Moglie Le Quintrec, MD, and Jean Louis Vanherweghem M. Herbs and the kidney. Am J Kidney Dis. 2004;44(1):1–11.
5. Awodele O, Daniel A, Popoola TD, Salami EF. A study on pharmacovigilance of herbal medicines in Lagos west Senatorial District, Nigeria. Int J Traf Saf Med. 2013;25(4):205–17.
6. Skalli S, Benchekih RS. Pharmacovigilance of herbal medicines in Africa : questionnaire study. J Ethnopharmacol. 2015;171:99–108.
7. Debbie S, Graeme L, Pierre D, Elizabeth W, Kelvin C. Pharmacovigilance of herbal medicine. J Ethnopharmacol. 2012;140(3):513–8.
8. Lehmann H, Pabst J. La phytovigilance : impératif médical et obligation légale. Ann Pharm Fr. 2015:1–12.
9. Barnes J. Pharmacovigilance of Herbal Medicines A UK Perspective. Drug Sade. 2003;26:12.
10. WHO. guidelines on safety monitoring of herbal medicines in pharmacovigilance systems. World Health Organization, Geneva. 2004.
11. Skalli S, David J, Palmer G. Botanicus et Phytotox : base de données de toxicologie végétale. Intérêt en toxicologie d’ urgence et en phytovigilance. Therapie. 2006;61(1):133–7.
12. C. A. Navarro, U. Busto, Pharm.D., M.D., Ph.D., P. Sandor, M.D., J. Ruiz, Pharm.D., E. A. Roberts, M.D., E. Janecek, Bsc. Pharm., C. Dorneqcm, Pharm. D,and D. J. Greenblatt. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981;30(2):239–245.
13. Touiti N, Achour S, Iken I, Chebaibi M, Houssaini TS. Nephrotoxicity associated with herbal medicine use , experience from Morocco. Toxicol Anal Clin. 2019;53(1):145–52.
14. Kim HY, Kim SS, Bae SH, Bae EH, Ma SK, Kim SW. Acute interstitial nephritis induced by Dioscorea quinqueloba. BMC Nephrol. 2014;15(1):1–5.
15. Kang K, Heo ST. A case of life-threatening acute kidney injury with toxic encephalopathy caused by Dioscorea quinqueloba. Yonsei Med J. 2015;56(1):304–8.
16. Kim CS, Kim SM, Choi JS, Bae EH, Kim SW. Dioscorea Quinqueloba induces acute kidney injury : two case reports. J Clin Toxicol. 2011;12(5):2–6.
17. Luycx VA, Ballantine R, Claës M, Cuycens F, Van Den Heuvel H, Cimanga RK, et al. Herbal remedy–associated acute renal failure secondary to cape aloe. Am J Kidney Dis. 2002;39(3):31–5.
18. Veldcovit-radovanovic RM, Klich D, Kostic S, Cvetkovic T, Djordjevic V. Acute renal failure after Licorice ingestion : a case report. Cent Eur J Med Acute. 2010;6(1):113–6.
19. Adejumo OA, Akinbodewa AA, Ogurinleay A, Agoi OF, Abolarin OS. A case report of acute kidney injury following the use of herbal vaginal Pessary. African J Med Heal Sci. 2017:1665–7.
20. Ack D’Y, Yllmarz M, Sahin HH, Sayiner Z, Koruk I, Tiryaki O, et al. Case report Management of Chenopodium polyspermum toxicity with plasma exchange and Hemodialysis. J Clin Apher. 2012;27(2):278–81.
21. Atılan E, Sayın S, Demirbağ Ş, Çakar M, Somak NG. A case study report of acute renal failure associated with Nigella sativa in a diabetic patient. J Integr Med. 2013;11(1):64–6.
22. Ok ES, Hasnæsi K, Tatar E, Tosun A. Acute kidney injury induced by herbal products : a case report. Turk Neph Dial Transpl. 2014;4(3):256–8.
23. Özkân G, Uluoy S. A case of renal failure developing in association with African mango consumption. Int J Clin Exp Med. 2015;8(4):6374–8.
24. Khine YY. Acute kidney injury following ingestion of henna leaf extract : a case report from Myanmar. Blood Purif. 2017;44(suppl 1):41–5.
25. Qureshi HEA, Qumqumji AAA, Zacharia Y. Acute renal failure and intravascular Hemolysis following henna ingestion. Saudi J Kidney Dis Transplant. 2013;24(3):553–6.
