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Review Article

Renal Diseases and Use of Medicinal Herbal Extracts: A Concise Update of Reported Literature in Africa

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Abstract

Herbal-induced renal disease constitutes an important etiology of renal diseases in daily clinical practice. As up to 80% of the population in Africa is estimated to use herbal preparations, which are generally perceived as safe and free from adverse effects, this consumption however has been associated with 35% of all cases of acute kidney injury. Consumption of potentially toxic medicinal herbs, incorrect substitution of harmless herbs with toxic herbs, contamination with toxic compounds or interactions with conventional treatments are the major problems. The source, composition and preparations of these herbs vary on the prevalent local healing practices. Most herbs contain active compounds, however, they are not tested for efficacy and safety; the ingredients are not well known and the dosage and route of administration are not standardized. This paper reviews the reports on the use of herbal medicines and its association with renal injuries in Africa.

Keywords: Acute kidney injury; Africa; Chronic kidney disease; Herbal medicines

Introduction

Renal diseases may occur due to direct renal injury with acute tubular damage and acute interstitial nephritis or by indirect mechanism such as hemolysis and hypovolemic conditions [1]. Herbal related kidney injuries constitute important manifestation of renal disease in present clinical practice. In African countries, there are many potential causes of kidney diseases [2]. Despite, infection, chronic glomerulonephritis, hypertension and lately diabetes mellitus being dominant etiological factors of Chronic Kidney Disease (CKD) in Africa [1,3], traditional herbal medicines have been recognized to substantially contribute to the renal disease burden [4]. Considering a large proportion of people are consuming herbal remedies, it is likely that most do not experience acute renal complications [5]; however, the use of herbal remedies has been associated in 35% of all cases of acute renal failure in Africa, this figure is likely to be underestimate of the true picture because of the secrecy surrounding the traditional health practices and use of traditional remedies [6,7].

Kidneys are particularly susceptible to toxic substances because kidneys have large surface area, high blood flow, high metabolic activity and possible active reabsorption and concentrations of toxins. As such, diverse forms of kidney injuries have been associated with toxic substances. In addition, patients with or at risk of renal impairment are at increased risk to insults from such remedies [5,8]. The identities of toxic substances contained in African herbal medicines are largely unknown, and the toxicology and pathogenesis of these herbal preparations are unknown too [7].

The aim of this review is to discuss the evidence that 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.

Use of Herbal Medicines

Herbal preparations for therapeutic uses can be found in ancient literature and they continue to form the backbone of our pharmaceuticals in modern times; whereby more than 50% drugs used in conventional pharmacopeia are either isolated from herbs or isolated from chemicals once found in plants. Examples of drugs that were derived from plants but still used widely until today include digitalis and quinine [9]. Herbal medicines are extensively utilized in the developing world, where in many places they offer a more widely available and more affordable alternative to conventional therapies. In Africa, for example, up to 80% of the population depends on them. Herbal medicines are also popular in developed countries [10]. WHO estimates that 50% of Canadians and 75% of people in France have tried Complementary or Alternative Medicine (CAM), which often includes medicinal herbal preparations. In Japan, for example 85% of doctors prescribe not only orthodox medicine but also herbal medicine (called Kampo), which are covered by health insurance [10].

Wide spread human exposure to a variety of chemicals and recent awareness of their toxic manifestations has led to the recognition of toxic nephropathy as an important segment of renal disease. Some of the nephrotoxins are derived from plants, whereby these plants are used to prepare medicines for various ailments. The spectrum of exposure varies from country to country and even from community to community, depending on variations in the distribution of local plants and prevalent social practices. Herbal medicines constitute a special class of nephrotoxins among several communities in Africa [11].

Herbal preparations tend to vary in its consistency in composition and biological activity due to problems in plants identification, differences in extracts processing and lack of information of pharmacological active compounds. The prevalence of renal diseases caused by traditional herbal medicines is directly related to a

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combination of several factors and widespread beliefs in indigenous systems of medicine in rural areas [12].

Herbal Medicine Toxicity

Despite numerous reports of toxicity by plants and herbal preparations, most literature is based on the experience in developed countries [13,14]. Clustering of cases after exposure to a particular agent suggests the possibility of a toxic insult. Botanical toxins are encountered both in common edible plants (i.e., djenkol beans, mushrooms) and medicinal herbs (i.e., impila, cat's claw). Mistaken identification of medicinal herbs frequently leads to toxicity. Late presentation and multi-organ dysfunction are associated with a high morbidity and mortality [11].

Kidney Injuries due to Herbal Medicines

Numerous literatures show that Acute Renal Injury (AKI) is potentially the most life threatening complication resulting from herbal preparations. The use of herbal preparations accounts for nearly 35% of all cases of AKI in Africa [7]. Most of nephrotoxicity reports due to herbal remedies in Africa are from southern Africa. Nephrotoxic effects can result from consumption of potentially toxic herbs, incorrect identification or substitution of non-toxic herbs with toxic herbs, contamination with non-herbal toxic compounds or when these herbs interact with prescribed conventional therapies [9]. Herbal preparations could be the covert source of potassium in patients with renal diseases especially in the presence of concurrent use of with Angiotensin Converting Enzyme (ACE) inhibitors [15]. Toxins from herbal preparations may cause AKI, tubular dysfunction, electrolyte imbalances, hypertension, renal papillary necrosis, urolithiasis and Chronic Kidney Disease (CKD) [4].

Despite the reports that herbal preparations from regions of Africa contain nephrotoxic compounds, only few herbal plants and preparations have been identified. Renal failures resulted in most of the cases were from tubular necrosis. It may be a sole abnormality or may be associated with acute gastroenteritis, hepatic failure, acute hemolysis, disseminated intravascular coagulation and neurological disorders.

Kidneys play an intrinsic role and often receive 25% of the cardiac output that contains high amount of metabolically active substances. Renal tubules actively reabsorb, secrets and/or concentrates substances in renal tubules, interstitial and luminal fluid. This makes tubular cells particularly vulnerable to direct toxic insults [25]. In the setting of renal disease or volume depression, concentration of toxic substances per nephron and duration of exposure tend to increase and cause more nephron damage [26].

Atractyloside, a toxin extracted from Impila; ox-eye daisy (*Callilepsis laureola*) plant is believed to inhibit mitochondrial oxidative phosphorylation, which leads to apoptosis and necrosis of tubular cells [16]. Extracts from violet tree; wild wisteria (*Securidaca longepedunculata*) contains salicylates, which can cause ischemic renal damage by inducing renal vasoconstriction [5].

For most of African traditional herbal preparations, the components of the many plants/remedies remain unknown, the potential mechanisms by which they cause toxic effects has not been studied, although or the information and evidence is currently growing.

The following section describes some of the medicinal plants (herbal preparations) that have been reported to cause renal damage.

***i) Cape aloe* (Aloe capensis)** is used extensively in South Africa and is generally not considered to be toxic. Cape aloes is a known laxative, used for hypertension, eczema, arthritis and stress. It contains Aloins A and B and their corresponding primary glycosides named aloinoisonides (Table 1). Aloe compounds have been implicated to cause parenchymatous nephritis and autopsy studies have revealed renal damage by causing acute tubular necrosis, suggesting that renal injury is due to dehydration.The exact pathogenesis of renal injury is unclear. In a case study, a black adult male patient presented with Acute Renal Failure (ARF) after consumption of aloe preparations by mouth at least 3 times before acute attack of oliguria [7,9]. Another adult male black patient was also diagnosed with ARF after ingesting an aloe containing preparations, the renal biopsy revealed the signs of acute interstitial nephritis [32].

ii) Callilepis laureola is the tuberous herb that grows widely in sub Saharan Africa. In South Africa is commonly known by Zulu name "Impila", meaning health. An extract of the tubers is taken orally, as an enema or as a douche. It is used to treat a number of conditions, however, it has been associated with marked hepatic and renal toxicity. The cases of Impila-induced renal toxicity emerged in medical literature during the 1970s. A case reported by Seedat and Hithlock [33] indicates that dosage is to blame in the toxicity of Impila. In this case report, an adult male patient developed hyperkalaemia and acute renal failure after ingestion if *C. laureola*. The renal damage caused is characterized by acute proximal convoluted tubule and loop of henle necrosis, which can lead to kidney failure [20]. The precise mechanism of renal injury is not clear but the toxic principle is thought to be the atractyloside, an alkaloid that inhibit the movement of Adenosine Diphosphate (ADP) across the mitochondrial membrane, preventing the synthesis of Adenosine Triphosphate (ATP) and causing renal cell death [7] (Table 1).

iii) Violet tree; wild wisteria (*Securidaca longepedunculata)* is a savannah shrub commonly used traditional herbalists. Herbal preparations of violet tree are commonly used for the treatment of dysmenorrhea, venereal diseases as well as an expectorant and abortifacient. The root of this plant has been found to contain methyl salicylate, which is thought to be nephrotoxic responsible for the AKI [21]. Another class of toxins from this plant is saponins, which are claimed to be toxic principle [22]. During autopsy, the kidneys show paleness with cortical petechiae [22]. Kidney histology of treated rats showed features consistent with renal epithelial injury from toxins [23] (Table 1).

iv) African mango (*Irvingia gabonensis)* is a regional leaf plant grown in tropical forests in West Africa. It is widely used in West African cuisine and produced commercially. Herbal preparations from this plant are commonly consumed in Africa for its ability to reduce weight [24], treating diarrhea diseases as well as skin diseases. In one case, a patient was reported to develop rapidly progressing renal failure after consumption of herbal preparations from this plant [25] (Table 1).

v) Khat leaf *(Catha edulis*), Catha edulis Forsk is a small to medium sized green tree cultivated mainly in Eastern and horn of Africa. Chewing Khat leaf for its psychostimulatory effect is a common habit of East African people. Nephrotoxicity has been observed in experimental animals. Following in vivo administration of Khat extracts, histologic examination of rabbit's kidneys revealed dose related lesions, with fat droplets in the upper cortical tubules. Acute tubular nephrosis was also observed (Table 1) [26-28]. In rats,

male and female Sprague-Dawley rats (n=24) received a single daily dose of crude extracts of Khat suspended in distilled water according to body weight. Microscopic examination of kidney sections of female rats showed different degrees of histopathological changes according to dose level. Such changes were characterized by atypical tubules, amorphous Malpighian corpuscles, and invasive infiltrative inflammatory cells. The glomerular capillaries in Malpighian corpuscles were destructed and hypertrophied [29]. In the other study, high dose Khat was shown to induce mild to moderate renal damage and significantly accentuated the gentamicin- induced renal damage in rats [30].

Plant name	Origin	Renal manifestation	Indications	Toxic compound	References
Cape aloe (Aloe capensis)	South Africa	Parenchymatous nephritis	Laxative	Aloins and Aloinosides	[7,9,27]
Impila; Ox-eye daisy (Callilepsis laureola)	South Africa, Swaziland	Necrosis of convoluted tubules and loop of henle	Vermicide, Decongestat, importance, To fight evil spirits	Atractyloside, Carboxyatractyloside	[7,16,27]
*Khat leaf (Catha edulis)	Horn of Africa, East Africa	Dose related lesions on upper cortical tubule, Acute tubular necrosis	Stimulant (Management of obesity and depression)	S-cathinone	[26,27,38]
Yam (Dioscorea quartiniana)	Zimbabwe	AKI	Staple food, Antidiuretic, anesthetic	Dioscorine and dioscine	[27]
Wild wisteria; Violet tree (Securidacea longepedunculata)	Tanzania, Malawi, Sudan, Burkina Faso, Congo, Zambia, Zimbabwe	Cortical necrosis, Acute interstitial nephritis	Dysmenorrhea, Venereal diseases, Laxative, Expectorant, Abortifacient, Snakebites	Methylsalicylate, Securinine, Saponins	[21-23,28]
African mango (Irvingia gabonensis)	West Africa	CKD	Weight Reduction, Diarrhea, Dysentery	Unknown	[24,25]
Bird flower (Crotalaria laburnifolia)	Zimbabwe	AKI	Dysmenorrhea, Abortifacient	Unknown	[28]
Euphorbiaceae (Euphorbia paralias)	Mediterranean region (Egypt, Tunisia)	Tubular necrosis, Interstitial nephritis	Local anesthesia, Purgative	Unknown	[31]

Table1: Summary of the reports of kidney injuries due to herbal medicines in Africa.

*Effects were reported in experimental animals; AKI refers to acute kidney injury; CKD refers to chronic kidney disease.

vi) Yam (*Dioscorea quartiniana*) (Table1) is a tuberous plant, commonly used as staple dietary component. In dietary use, the tubers are either placed in running water for few days, soaked in salt water, roasting or boiling for several hours to remove toxins before eating. Poisoning is usually a result of improperly prepared tubers in cases of famine or after medical use. Renal failure is thought to occur because of toxins, dioscorine and dioscine [27].

vii) Euphorbiaceae *(Euphorbia paralias)* (Table 1) is a hardy plan that inhabits the entire Mediterranean region. Fisherman commonly uses this plant as local anesthetic in cases of fish bites, is also used in human medicine as purgative. This plant was thought to be a causative of progression of kidney disease whereby patient developed massive proteinuria and AKI. The AKI was due to a severe tubular necrosis. However, the exact mechanism of the toxicity is not known [31].

Interactions Between Herbal Medicines and Conventional Drugs

Due to the fact that herbal preparations contain complex mixtures of active ingredients, this multitude if ingredients increase the possibilities of interaction between herbal and conventional drugs [32]. Patients often combine prescription medications with herbal remedies. The danger of combining medicinal herbs and conventional drugs is always warranted, because of the potential interactions between active ingredients. Interactions between herbal medicines and conventional drugs may either increase or decrease the pharmacological effects of the drug. The increase of the of compounds effects to toxic levels. Synergistic therapeutic effects may also complicate the dosing regimen especially in long-term therapies [33].

The well-described potentially worst example of herb-drug interaction is that of St John's wort (*Hypericum perforatum*) a native plant to parts of Europe and Asia but has spread worldwide as a cosmopolitan invasive weed. Is popular medicinal herb used for the treatment of depression and substrates of cytochrome P450 CYP 3A4 isoenzymes. One of the cytochrome P450 CYP 3A4 substrate is cyclosporine, a commonly used immunosuppressant. Concurrent administration of cyclosporine and St John's wort results in the rapid metabolism of immunosuppressant rendering it useless [34,35]. The true prevalence of herbal medicines and conventional medications interactions amongst patients with renal diseases is substantial but unknown, experimental data in the field of herbal medicine and conventional medicines interactions in Africa however is very limited. Despite the paucity of this type of literature in Africa, there are many indications that this problem exists, which subsequently requires the need for much needed studies. For the time being, the very least we should do is to follow the advice of authors from developed countries who concluded that any use of medicinal herbs is inappropriate for the renal patient if not all patients [30].

Adulteration of Herbal Preparations

Adulteration is the substitution of the original crude drug partially or fully with other substances which is either free from or inferior in therapeutic and chemical properties. Adulteration of an article may be intentional or accidental. The crude preparations are substituted with other compounds as adulterant which may or may not have any therapeutic potential as that of original compound.

There is growing awareness of "generic" products being substituted for rare medicines, safely or not. Medicinal extracts are replaced by different compounds, notably ingredients prepared in powdered form, which can stay for longer without spoilage [37].

Adulteration has been documented in Chinese herbal medicines where more than 48 cases of renal poisoning related to Fang-Ji (*Stephania tetrandra*) in a weight loss preparation were caused by

Guangfang-Ji (*Aristolochia fangchi*): aristolochic acid is a known nephrotoxin [38].

There are not many reports of deliberate adulteration of herbal remedies in Africa. However, addition of conventional pharmaceutical agents to herbal preparations in Africa has been recently reported in 2 cases of toxicity after the ingestion of traditional herbal medicines, and after analysis of the preparations, several conventional compounds were detected. In the first case, trimethadione, a drug used for treatment of petit mal seizures was identified. It has a number of interactions with other anticonvulsants, antidepressants, contraceptives and vitamins. In the second case, propofol, an anesthetic agent and diclofenac, a nonsteroidal anti-inflammatory agent were identified in the herbal preparations [39].

The case of incorrect identification was reported in Morocco and Sudan where the toxic compound Takaoutroumia, a paraphenylenediamine was substituted for Taka out El badia, a traditionally made from *Tamaris orientalis* and used as a hair dye and in henna preparations, resulting in rhabdomyolysis and severe renal failure [5].

Conclusion

In a view of the current literature, it is evident that the consumption of herbal remedies is a common phenomenon in large part of Africa. Despite the mythical yet dominant view that herbal remedies are free from side effects because they are natural, literature and facts presented in this review signify that herbal medicines may exert renal toxicity through their inherent properties, making them unsafe both, for individual's general health as well as to the kidney health. One cannot blame all herbal medicines to cause renal injury, however, renal diseases caused by consumption of herbal preparations should be considered in patients with unexplained kidney disease patient education on herbal and kidney health, physician awareness and continued surveillance are required to tackle the growing problem. A current challenge is to re-evaluate phytotherapy practices, some of which date back 2000 years. Importantly, specific information on herbal toxicity and herbal-drug interactions, both renal and general is lacking. Another challenge we need to address is to create openness in the doctor-patient discourse and encourage the confidence of healthcare seekers to discuss their desire to use herbal preparations or alternative therapies. This review was limited to the most commonly used medicinal plants and information from plants available in Africa.

Authors' Contribution

ACL conceived and designed the review. Both ACL and HMJ collected and analyzed literatures, wrote the review to the final manuscript. All authors approved the final version of the manuscript.

Competing Interest

The authors declare no conflict of interests.

References

1. Naicker S, Aboud O, Gharbi MB (2008) Epidemiology of acute kidney injury in Africa. Semin Nephrol 28: 348-353.
2. Stanifer JW, Jing B, Tolan S, Helmke N, Mukerjee R, et al. (2014) The epidemiology of chronic kidney disease in sub-Saharan Africa: a systematic review and meta-analysis. Lancet Glob Health 2: 174-181.
3. Okunola O, Akinsola A, Ayodele O (2012) Kidney diseases in Africa: aetiological considerations, peculiarities and burden. Afr J Med Med Sci 41: 119-133.
4. Jha V, Garcia-Garcia G, Iseki K, Li Z, Naicker S, et al. (2013) Chronic kidney disease: global dimension and perspectives. Lancet 382: 260-272.
5. Luyckx VA (2012) Nephrotoxicity of alternative medicine practice. Adv Chronic Kidney Dis 19: 129-141.
6. Isnard Bagnis C, Deray G, Baumelou A, Le Quintrec M, Vanherweghem JL (2004) Herbs and the kidney. Am J Kidney Dis 44: 1-11.
7. Luyckx VA, Ballantine R, Claeys M, Cuyckens F, Van den Heuvel H, et al. (2002) Herbal remedy-associated acute renal failure secondary to Cape aloes. Am J Kidney Dis 39: 13.
8. Colson CR, De Broe ME (2005) Kidney injury from alternative medicines. Adv Chronic Kidney Dis 12: 261-275.
9. Jha V, Rathi M (2008) Natural medicines causing acute kidney injury. Semin Nephrol 28: 416-428.
10. Aschwanden C (2001) Herbs for health, but how safe are they? Bulletin of the World Health Organization 79: 691-692.
11. Jha V, Chugh KS (2003) Nephropathy associated with animal, plant, and chemical toxins in the tropics. Semin Nephrol 23: 49-65.
12. Marcus DM, Grollman AP (2002) Botanical medicines--the need for new regulations. N Engl J Med 347: 2073-2076.
13. Huxtable RJ (1990) The harmful potential of herbal and other plant products. Drug Saf 5 : 126-136.
14. Bernstein JN (1994) Common plant ingestions. J Fla Med Assoc 81: 745-746.
15. Mueller BA, Scott MK, Sowinski KM, Prag KA (2000) Noni juice (Morinda citrifolia): hidden potential for hyperkalemia? Am J Kidney Dis 35: 310-312.
16. Luyckx VA, Naicker S (2008) Acute kidney injury associated with the use of traditional medicines. Nat Clin Pract Nephrol 4: 664-671.
17. Debelle FD, Nortier JL, De Prez EG, Garbar CH, Vienne AR, et al. (2002) Aristolochic acids induce chronic renal failure with interstitial fibrosis in salt-depleted rats. J Am Soc Nephrol 13: 431-436.
18. Gold CH (1980) Acute renal failure from herbal and patent remedies in Blacks. Clin Nephrol 14: 128-134.
19. Seedat YK, Hitchcock PJ (1971) Acute renal failure from *Callilepsis laureola*. S Afr Med J 45: 832-833.
20. Stewart MJ, Steenkamp V, van der Merwe S, Zuckerman M, Crowther NJ (2002) The cytotoxic effects of a traditional Zulu remedy, impila (*Callilepis laureola*). Hum Exp Toxicol 21: 643-647.
21. Watt JM, Breyer-Brandwijk MG (1962) The Medicinal and Poisonous Plants of Southern and Eastern Africa, (2nd edn), Livingstone, London.
22. Neuwinger HD (1996) African Ethnobotany: Poisons and Drugs, Chapman and Hall, London.
23. Dapar LPM, Aguiyi JC, Wannang NN, Gyang SS, and Tanko MN (2007) The histopathologic effects of *Securidaca longepedunculata* on heart, liver, kidney and lungs of rats. Afr J Biotech 6: 591-595.
24. Ngondi JL, Etoundi BC, Nyangono CB, Mbofung CM, Oben JE (2009) IGOB131, a novel seed extract of the West African plant *Irvingiaga bonensis*, significantly reduces body weight and improves metabolic parameters in overweight humans in a randomized double-blind placebo controlled investigation. Lipids Health Dis 8: 7.
25. Özkan G, Ulusoy S (2015) A case of renal failure developing in association with African mango consumption. Int J Clin Exp Med 8: 6374-6378.
26. Al-Mamary M, Al-Habori M, Al-Aghbari AM, Baker MM (2002) Investigation into the toxicological effects of *Catha edulis* leaves: a short term study in animals. Phytother Res 16: 127-132.
27. Steenkamp V, Stewart MJ (2005) Nephrotoxicity associated with exposure to plant toxins, with particular reference to Africa. Ther Drug Monit 27: 270-277.

28. Kamsu-Foguem B, Foguem C (2014) Adverse drug reactions in some African herbal medicine: literature review and stakeholders' interview. Integr Med Res 3: 126-132.

29. Alsalahi A, Abdulla MA, Al-Mamary M, Noordin MI, Abdelwahab SI, et al. (2012) Toxicological Features of *Catha edulis* (Khat) on Livers and Kidneys of Male and Female Sprague-Dawley Rats: A Subchronic Study. Evid Based Complement Alternat Med 2012: 829401.

30. Shewamene Z, Engidawork E (2014) Subacute administration of crude khat (Catha edulis F.) extract induces mild to moderate nephrotoxicity in rats. BMC Complement Altern Med 14: 66.

31. Boubaker K, Ounissi M, Brahmi N, Goucha R, Hedri H, et al. (2013) Acute renal failure by ingestion of *Euphorbia paralias*. Saudi J Kidney Dis Transpl 24: 571-575.

32. Ernst E (2000) Herb-drug interactions: potentially important but woefully under-researched. Eur J Clin Pharmacol 56: 523-524.

33. Fugh-Berman A (2000) Herb-drug interactions. Lancet 355: 134-138.

34. Moschella C, Jaber BL (2001) Interaction between cyclosporine and Hypericum perforatum (St. John's wort) after organ transplantation. Am J Kidney Dis 38: 1105-1107.

35. Bauer S, Störmer E, Johne A, Krüger H, Budde K, et al. (2003) Alterations in cyclosporin A pharmacokinetics and metabolism during treatment with St John's wort in renal transplant patients. Br J Clin Pharmacol 55: 203-211.

36. Foote J, Cohen B (1998) Medicinal herb use and the renal patient. J Ren Nutr 8: 40-42.

37. Fennell CW, Lindsey KL, McGaw LJ, Sparg SG, Stafford GI, et al. (2004) Assessing African medicinal plants for efficacy and safety: pharmacological screening and toxicology. J Ethnopharmacol 94: 205-217.

38. But PP (1994) Herbal poisoning caused by adulterants or erroneous substitutes. J Trop Med Hyg 97: 371-374.

39. Snyman T, Stewart MJ, Grove A, Steenkamp V (2005) Adulteration of South African traditional herbal remedies. Ther Drug Monit 27: 86-89.