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...
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, secrete 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 (*Callilepis 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/medicines 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 aloe is a known laxative, used for hypertension, eczema, arthritis and stress. It contains Aloins A and B and their corresponding primary glycosides named aloinoids (Table 1). Aloinoids 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 Hithlcock [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].

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 amongst patients with renal diseases is substantial but complicated 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 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 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 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 or fully with other substances which is either free from or inferior in therapeutic and chemical properties.
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


