Nephrotoxicity of herbaltreatments: riskfactors, mechanisms and implications for clinical practice

[Nephrotoxicity of herbal treatments: risk factors, mechanisms and implications for clinical practice]

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ABSTRACT: The global use of herbal treatments continues to expand, largely driven by the belief that natural products are inherently safe. However, growing scientific evidence shows that many herbal preparations possess nephrotoxic potential. This article examines the risk factors associated with herb-induced kidney injury, including prolonged self-medication, poor product quality, contamination with heavy metals or pharmaceuticals, and harmful herb such as direct cytotoxicity from compounds like aristolochic acid, immune-mediated reactions, and tubular or obstructive renal damage. The review emphasizes the need for systematic clinical monitoring, strengthened phytovigilance, and improved patient and healthcare professional education to mitigate risks. It concludes by calling for stricter regulatory frameworks and further research to better characterize the toxic constituents of herbal products and ensure their safe clinical use.

KEYWORDS: Nephrotoxicity , Herbal medicine ,Aristolochic acid , Phytovigilance , Herb–drug interactions

RESUME: L'utilisation des traitements à base de plantes continue de se développer à l'échelle mondiale, principalement en raison de la croyance en l'innocuité intrinsèque des produits naturels. Cependant, de plus en plus de données scientifiques démontrent la néphrotoxicité potentielle de nombreuses préparations à base de plantes. Cet article examine les facteurs de risque associés aux lésions rénales induites par les plantes, notamment l'automédication prolongée, la mauvaise qualité des produits, la contamination par des métaux lourds ou des médicaments, et la toxicité de certaines plantes, comme la cytotoxicité directe de composés tels que l'acide aristolochique, les réactions à médiation immunitaire et les lésions tubulaires ou obstructives rénales. Cette revue souligne la nécessité d'une surveillance clinique systématique, d'une phytovigilance renforcée et d'une meilleure formation des patients et des professionnels de santé afin de limiter les risques. Elle conclut en appelant à des cadres réglementaires plus stricts et à des recherches supplémentaires pour mieux caractériser les constituants toxiques des produits à base de plantes et garantir leur utilisation clinique en toute sécurité.

MOTS-CLEFS: Néphrotoxicité, phytothérapie, acide aristolochique, phytovigilance, interactions plantes-médicaments

1 INTRODUCTION

The use of herbal remedies (HR) is an ancient practice that continues to thrive and expand within modern healthcare systems. According to the World Health Organization (WHO, 2019), approximately 80% of the global population relies on traditional medicine, with herbal therapy representing a significant component. This widespread use is often driven by a preference for “natural” treatments, skepticism toward conventional medicine, cultural influences, or limited access to formal healthcare services (Ekor, 2014).

However, the perception that herbal products are inherently safe is a misleading and potentially dangerous assumption. Plants synthesize a vast array of secondary metabolites with potent pharmacological effects, which under certain conditions or at specific doses may exhibit hepatotoxic, neurotoxic, or nephrotoxic properties (Jordan & Cunningham, 2011). Nephrotoxicity linked to herbal medicine use poses a growing clinical and diagnostic challenge for nephrologists and other healthcare providers. This challenge is further compounded by insufficient regulatory oversight of many herbal products, significant variability in their composition and active ingredient concentrations, and a general lack of awareness regarding their potential mechanisms of toxicity (Graham et al., 2020)

This article aims to present a thorough and current review of the nephrotoxicity associated with herbal-based treatments. It will examine the epidemiological background, key risk factors, and underlying pathophysiological mechanisms, concluding with practical recommendations for clinical practice and public health policy.

2 PREVALENCE AND EPIDEMIOLOGICAL CONTEXT

Accurately estimating the prevalence of nephrotoxicity linked to herbal products is challenging due to significant underreporting. Many cases remain undiagnosed, are misattributed to other causes, or are not documented in pharmacovigilance systems (Debelle et al., 2008). Despite these limitations, existing evidence points to a concerning trend.

Regional studies highlight the scope of this issue. A recent investigation in eastern Morocco revealed that 71.5% of patients with end-stage renal disease receiving chronic hemodialysis had a history of medicinal plant use. Commonly implicated species included Aristolochia longa (“Berraztam”), Artemisia herba-alba (“Chih”), Rhamnus alaternus (“Ghart”), and Rubia tinctorum (“Fouwwa”) (Selles et al., 2024). This association suggests a potential causal role in the development of chronic kidney disease within this population.

A systematic review of pharmacovigilance data identified 27 confirmed cases of nephrotoxicity directly associated with medicinal plants and an additional 44 cases linked to dietary supplements—many of which contain botanical extracts—over a specified period (Posadzki et al., 2013). Although these numbers may appear limited, they likely represent only a fraction of actual occurrences. The true incidence is probably substantially higher, especially in regions where traditional medicine is widely practiced and regulatory oversight is less stringent (Chen & Wang, 2023).

The epidemiology of herbal nephrotoxicity is further illustrated by historical outbreaks. The most notable is the 1990s Belgian case series termed “Chinese herbal nephropathy,” in which hundreds of patients developed progressive interstitial nephropathy and urothelial carcinomas following consumption of weight-loss supplements containing Aristolochia fangchi (Nortier et al., 2000). Similar incidents have been reported globally, prompting the World Health Organization to issue alerts regarding plants belonging to the Aristolochia genus

3 RISK FACTORS FOR NEPHROTOXICITY

The occurrence of kidney damage related to RBP is not random; it is promoted by several interdependent risk factors.

3.1. PROLONGED USE AND SELF-PRESCRIPTION

The absence of medical supervision represents a primary risk factor. Patients frequently engage in self-medication driven by cultural practices, recommendations from relatives, or information obtained from non-scientific sources such as the internet or magazines. Prolonged use without professional guidance or monitoring can lead to the accumulation of toxic compounds, surpassing the body's detoxification capabilities and resulting in chronic, often irreversible, renal injury (Yang et al., 2018). Vulnerable groups are at particularly high risk

3.2. PRODUCT QUALITY AND PRESENCE OF CONTAMINANTS

In contrast to allopathic medicines, many herbal-based products (HBP) are not governed by stringent regulations pertaining to manufacturing standards, quality control, purity, or dosage. This regulatory gap introduces significant risks, including: Heavy metal contamination: Preparations—especially those used in Ayurvedic or traditional medicine—may be intentionally or inadvertently contaminated with heavy metals such as lead, mercury, arsenic, or cadmium. A meta-analysis found that nearly 20% of Ayurvedic products marketed online contained dangerous levels of these metals (Saper et al., 2008). More recent investigations confirm that a substantial proportion of herbal products remain contaminated with toxic elements (Genuis et al., 2022). These metals act as potent nephrotoxins, contributing to tubulopathies and interstitial

fibrosis. Adulteration with pharmaceutical drugs: To enhance perceived efficacy, some so-called “natural” products are illicitly adulterated with active pharmaceutical ingredients—including NSAIDs, corticosteroids, diuretics, and phosphodiesterase-5 inhibitors. Their undisclosed presence exposes consumers to inherent side effects and potential drug interactions (Graham et al., 2020). Microbiological and pesticide contamination: Additional risks include the presence of mold, bacteria, or pesticide residues, which may further contribute to toxicological effects.

3.3. Drug Interactions and Dosage Errors

Herbal remedies can significantly influence the pharmacokinetics of conventional pharmaceutical agents, potentially amplifying their toxicity. Certain botanicals, such as St. John's Wort, act as potent inducers of cytochrome P450 enzymes, accelerating the metabolism of co-administered drugs and diminishing their therapeutic efficacy. Conversely, other herbs may compete with medications for protein binding sites or renal excretion pathways, thereby elevating plasma concentrations to hazardous levels (Izzo et al., 2016; Izzo & Ernst, 2023). Furthermore, the absence of standardization and reliance on empirical dosing in artisanal preparations can result in the consumption of excessively high doses of active compounds, frequently surpassing established safety limits.

4 Mechanisms of Nephrotoxicity

The nephrotoxicity of RBP can occur via several pathophysiological mechanisms, which are sometimes intertwined.

4.1. Direct Toxicity of Active Ingredients

Numerous plant-derived compounds exhibit direct cytotoxic effects on renal structures, particularly targeting tubular cells. Among the most well-documented nephrotoxins is aristolochic acid (AA), found in plants of the genera Aristolochia and Asarum. Following metabolic activation, AA forms persistent DNA adducts within renal cells, leading to fibrosing interstitial nephropathy that often progresses to end-stage renal disease. Additionally, AA exposure significantly increases the risk of developing urothelial carcinoma of the upper urinary tract (Grollman, 2013). The pathogenic mechanism involves both tubular necrosis and activation of profibrotic pathways.

Anthraquinones, present in laxative botanicals such as senna (Senna alexandrina), buckthorn (Rhamnus frangula), and aloe (Aloe vera), can induce vacuolar degeneration in renal tubules. Chronic consumption is associated with "anthraquinone nephropathy," a condition characterized by cortical atrophy and interstitial fibrosis (Yang et al., 2018).

4.2. Immunoallergic and Inflammatory Reactions

Certain botanical agents can induce nephrotoxicity through immune system activation rather than direct cytotoxic effects, particularly at lower doses. Acute Interstitial Nephritis (AIN) represents a T-cell-mediated hypersensitivity reaction characterized by inflammatory infiltration of the renal interstitium, frequently resulting in oliguric acute kidney injury. Salles et al. (2024) reported a case of severe AIN in an adolescent following ingestion of a herbal mixture containing *Artemisia absinthium*, *Marrubium vulgare*, and *Centaurium erythraea*. Renal biopsy revealed interstitial inflammatory infiltrates in the absence of immunoglobulin deposits, consistent with a cell-mediated immune response. Although AIN is typically reversible upon discontinuation of the offending agent, delayed diagnosis may result in permanent renal impairment.

4.3. Tubular and Obstructive Damage

Additional pathophysiological mechanisms contribute to plant-associated nephrotoxicity: Acute Tubular Necrosis (ATN): As with pharmaceutical agents, certain botanicals can cause direct damage to renal tubular cells, resulting in necrosis and subsequent acute kidney injury. Crystalluria and Obstructive Nephropathy: Plants with high oxalate content—such as some species of Rumex or Hibiscus—may promote the precipitation of calcium oxalate crystals within renal tubules. This can lead to tubular obstruction and acute kidney injury through mechanical blockage (Jiang et al., 2017). Hydro-Electrolytic Imbalances: Botanicals with potent diuretic or laxative properties can induce significant fluid losses and electrolyte disturbances—including hypokalemia and hyponatremia. These imbalances may secondarily cause functional renal impairment or predispose to tubular necrosis through renal hypoperfusion and ischemic injury.

5 Implications for Clinical Practice

In light of this risk, a proactive and systematic approach by healthcare professionals is imperative.

5.1. The Importance of a Detailed and Non-Judgmental Medical History

A systematic and non-judgmental patient history is fundamental to both prevention and diagnosis. Inquiring about the use of herbal products should be a routine component of every clinical assessment, particularly for patients presenting with unexplained impaired renal function. Questions should be open-ended and neutrally phrased—such as, “Do you use any herbal products, teas, dietary supplements, or traditional remedies?”—to reduce the likelihood of patients concealing usage due to fear of criticism (Cohen & Ernst, 2010).

5.2. Adaptive Biological Monitoring

For any patient regularly using herbal-based products (HBPs), regular monitoring of renal function is recommended. This should include, at minimum, measurement of serum creatinine (with estimated glomerular filtration rate) and urinalysis by dipstick (assessing for proteinuria, hematuria, and leukocyturia). If abnormalities are detected, a prompt and comprehensive workup—including serum electrolytes, 24-hour urine protein quantification, urinary sediment examination, and nephrology consultation—should be initiated..

5.3. Strengthening Phytovigilance

It is essential to report any suspected adverse effects associated with herbal-based products (HBPs) to national pharmacovigilance systems. This process supports the development of evidence-based safety profiles, enables early detection of toxicity signals—including for less characterized botanicals—and facilitates appropriate regulatory actions such as usage restrictions or market recalls to safeguard public health. The World Health Organization emphasizes the need to strengthen regulatory oversight and surveillance mechanisms for traditional medicines (WHO, 2023). Healthcare providers should receive regular training to ensure awareness and compliance with these reporting protocols.

5.4. Education and Awareness for Patients and Professionals

Healthcare providers have a professional responsibility to correct the misconception that natural products are inherently safe. Effective, evidence-based, and empathetic communication regarding the potential risks of herbal products—including their toxicity, quality control issues, and potential for drug interactions—is essential. Clinicians can draw on recently published practical guides designed to support this educational role (Wojcikowski & Gobe, 2021). This outreach should also include pharmacists, who are frequently the first point of contact for patients purchasing these products and seeking advice regarding their use.

6 Conclusion

Nephrotoxicity resulting from herbal treatments represents a substantial yet often overlooked clinical concern. Contrary to popular belief in their harmlessness, many botanical preparations contain potent compounds that can induce acute or chronic renal impairment through diverse biological mechanisms including direct cellular toxicity, immune system activation, and metabolic interference. Effective risk mitigation requires an integrated, multidisciplinary strategy encompassing: enhanced clinical awareness through standardized patient screening protocols; tailored biochemical surveillance for vulnerable populations; reinforced phytovigilance programs to strengthen adverse event documentation; and sustained educational initiatives for both healthcare providers and consumers. Amid growing public interest in complementary and alternative therapies, there is an urgent need to advance evidence-informed, safety-conscious utilization of herbal products. Clinical practice should embrace a precautionary approach that acknowledges potential hazards while recognizing demonstrated benefits when products are used appropriately. Future research priorities should include improved characterization of toxic constituents, development of standardized manufacturing protocols, and more rigorous epidemiological risk assessment (Ramachandran & Kumar, 2023).

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