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Nephrotoxicity and Herbal Interventions: Mechanistic Insights and Safety Concerns

Bwanbale Geoffrey David

Faculty of Pharmacy Kampala International University Uganda

ABSTRACT

Nephrotoxicity, defined as structural and functional impairment of the kidneys due to chemical, biological, or metabolic insults, is a significant contributor to global morbidity and mortality. It arises from diverse causes including pharmaceutical agents, heavy metals, environmental toxins, infectious diseases, and metabolic conditions such as diabetes and hypertension. Pathophysiological mechanisms involve oxidative stress, mitochondrial dysfunction, inflammation, dysregulation of renal hemodynamics, and apoptosis/necrosis of tubular cells. Herbal medicines have been investigated both as protective interventions and, paradoxically, as causative agents of nephrotoxicity. Numerous phytochemicals-such as polyphenols, flavonoids, alkaloids, terpenoids, and saponins-exhibit antioxidative, anti-inflammatory, and cytoprotective activities, which may counter renal injury by modulating signaling pathways (Nrf2, NF-κB, TGF-β/Smad). Prominent candidates include curcumin, resveratrol, silymarin, quercetin, and berberine, as well as complex formulations from Ayurvedic, Chinese, and African traditional medicine. However, nephrotoxic risks arise from intrinsic phytochemical toxicity (e.g., aristolochic acids), adulteration with heavy metals, contamination, or herb-drug interactions. The duality of herbal remedies as potential nephroprotectants and nephrotoxins demands rigorous mechanistic research, standardized preparations, and long-term clinical trials. This review synthesizes current evidence on nephrotoxicity mechanisms, the protective role of herbal interventions, and the safety concerns critical to clinical translation.

Keywords: nephrotoxicity, herbal medicine, oxidative stress, renal protection, safety

INTRODUCTION

The kidneys are vital organs responsible for the filtration of metabolic waste, maintenance of electrolyte and fluid balance, regulation of blood pressure, and endocrine functions, including erythropoietin and vitamin D metabolism [1]. Their high perfusion rate, abundance of mitochondria, and exposure to circulating xenobiotics make them especially vulnerable to toxic injury [2]. Nephrotoxicity is an umbrella term encompassing acute kidney injury (AKI), chronic kidney disease (CKD) progression, tubular dysfunction, and glomerular pathology [2]. It is a major clinical challenge, contributing significantly to hospitalization, health-care costs, and mortality worldwide. Drugs such as aminoglycosides, cisplatin, NSAIDs, and radiocontrast media are classical nephrotoxicants [1,2]. Environmental pollutants-lead, cadmium, arsenic-further burden renal health, particularly in low-resource settings [3]. Additionally, lifestyle-related conditions such as diabetes and hypertension synergistically enhance susceptibility to nephrotoxic insults [4]. In parallel, the global popularity of herbal medicine continues to rise, fueled by cultural practices, affordability, and perceptions of safety. Phytochemicals derived from plants are widely used for renal and systemic conditions. Evidence from experimental studies suggests many herbs possess nephroprotective activity, often mediated through antioxidant and anti-inflammatory effects [5]. Yet, herbal products can also be sources of nephrotoxicity, either due to toxic constituents or poor manufacturing practices [6]. This review addresses both aspects: mechanisms of nephrotoxicity, herbal strategies to mitigate renal injury, and safety considerations essential for responsible use.

2. Mechanistic basis of nephrotoxicity

Nephrotoxicity arises from a network of interconnected mechanisms that compromise renal structure and function. One central pathway is oxidative stress, characterized by excessive production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) that overwhelm the kidney's intrinsic antioxidant defenses [7]. Tubular epithelial cells are particularly vulnerable due to their high mitochondrial content and metabolic activity [8]. ROS/RNS-

induced lipid peroxidation damages cell membranes, disrupts ion transport, and triggers DNA and protein modifications, ultimately impairing tubular reabsorption and filtration processes [9].

Mitochondrial dysfunction is both a source and a target of oxidative stress. Nephrotoxic agents such as cisplatin, aminoglycosides, and certain heavy metals disrupt the electron transport chain, cause mitochondrial swelling, and induce permeability transition, leading to ATP depletion [10]. Energy failure triggers cell death pathways, including apoptosis and necrosis, contributing to acute kidney injury [11]. Inflammatory responses further exacerbate renal injury. Damaged cells release damage-associated molecular patterns that activate NF-κB and inflammasomes, resulting in elevated cytokines such as TNF-α, IL-6, and IL-1β [12]. Recruitment of neutrophils, macrophages, and other immune cells amplifies tissue injury and promotes fibrotic remodeling [13]. Chronic inflammatory signaling can drive epithelial–mesenchymal transition and interstitial fibrosis, accelerating progression to chronic kidney disease [14].

Alterations in renal hemodynamics also play a significant role. Nonsteroidal anti-inflammatory drugs reduce prostaglandin synthesis, leading to vasoconstriction and decreased renal perfusion. Calcineurin inhibitors induce similar vasoconstriction via endothelin and renin–angiotensin system activation [15]. Medullary ischemia heightens vulnerability to hypoxic injury, which synergizes with oxidative stress to exacerbate tubular damage [16]. Ultimately, nephrotoxicity manifests through apoptosis, necrosis, and fibrotic changes. Acute insults primarily induce tubular cell death, while chronic exposures trigger maladaptive repair, fibroblast activation, and extracellular matrix deposition [17]. These mechanisms are not isolated; rather, they interact in complex feedback loops, highlighting multiple potential points for therapeutic intervention.

3. Herbal interventions: mechanistic insights into nephroprotection

Herbal medicines and phytochemicals provide multi-targeted strategies to mitigate nephrotoxicity, addressing oxidative stress, inflammation, mitochondrial dysfunction, and fibrosis simultaneously.

Many phytochemicals, including polyphenols such as quercetin, curcumin, and resveratrol, activate the nuclear factor erythroid 2–related factor 2 (Nrf2) pathway [18]. Nrf2 translocates to the nucleus and binds antioxidant response elements to upregulate enzymes such as superoxide dismutase, catalase, and glutathione peroxidase [19]. This enhances cellular antioxidant capacity, reduces lipid peroxidation, and preserves tubular integrity under toxic stress.

Anti-inflammatory effects are another key mechanism. Herbal compounds suppress NF-κB signaling, inhibit proinflammatory cytokine release, and downregulate enzymes such as cyclooxygenase-2 and inducible nitric oxide synthase [20]. Silymarin and berberine, for example, attenuate cytokine-mediated renal inflammation in experimental nephrotoxicity models [21].

Phytochemicals also stabilize mitochondria, preserving membrane potential, preventing permeability transition, and maintaining ATP synthesis. Resveratrol enhances mitochondrial biogenesis via SIRT1/PGC-1α pathways, while curcumin and ginsenosides support mitochondrial function, reducing energy failure and apoptosis in tubular cells [22].

Fibrotic signaling can be modulated by several herbal compounds. Inhibition of the TGF-β/Smad pathway prevents epithelial–mesenchymal transition and collagen deposition, thereby limiting interstitial fibrosis [23]. Andrographolide and silymarin have shown significant antifibrotic effects in experimental models [24]. Additionally, certain herbs improve renal hemodynamics through vasodilatory activity, often mediated by nitric oxide modulation [25]. Enhanced renal perfusion can protect the medulla from hypoxic injury and support glomerular filtration [25]. Collectively, these mechanisms illustrate the pleiotropic nature of herbal interventions. By simultaneously targeting oxidative stress, inflammation, mitochondrial integrity, fibrotic pathways, and renal perfusion, phytochemicals offer a multi-faceted approach to protect the kidneys from diverse nephrotoxic insults.

4. Representative herbal candidates

A growing body of research has identified several herbal medicines and phytochemicals with nephroprotective properties. These agents exert multi-targeted effects, including antioxidant, anti-inflammatory, antifibrotic, and mitochondrial-stabilizing activities, which collectively mitigate renal injury across different experimental and clinical contexts.

Curcumin, the principal bioactive compound of Curcuma longa, is widely studied for kidney protection. In preclinical models of cisplatin- and gentamicin-induced nephrotoxicity, curcumin reduces serum creatinine and blood urea nitrogen levels, preserves tubular architecture, and decreases oxidative stress markers such as malondialdehyde [26]. Mechanistically, curcumin activates Nrf2 signaling, suppresses NF-κB-mediated inflammation, and stabilizes mitochondrial function, preventing apoptosis [27]. Clinical studies in diabetic nephropathy also report improvements in oxidative stress parameters and modest reductions in proteinuria, although limited bioavailability remains a challenge.

Resveratrol, a stilbene found in grapes, berries, and peanuts, exhibits strong antioxidant and mitochondrial protective properties. It enhances SIRT1/PGC-1α-mediated mitochondrial biogenesis, reduces ROS generation, and inhibits proinflammatory cytokines in animal models of ischemia–reperfusion and diabetic nephropathy [28]. These actions preserve tubular cell viability and glomerular filtration [28]. Although human trials are sparse, early evidence suggests potential benefits in preventing progression of chronic kidney disease.

Silymarin, derived from Silybum marianum, contains flavonolignans such as silybin that provide membrane stabilization, free radical scavenging, and anti-fibrotic effects [29]. Experimental studies demonstrate that silymarin mitigates drug-induced tubular necrosis, reduces inflammatory cytokines, and inhibits TGF-β-driven fibrotic pathways [30]. Clinical trials in patients with chronic kidney disease show improved antioxidant status and reductions in markers of oxidative stress, supporting its translational potential [31].

Quercetin, a flavonoid abundant in fruits and vegetables, attenuates oxidative and inflammatory stress in gentamicin- and heavy-metal-induced nephrotoxicity [32]. By preserving mitochondrial membrane potential, suppressing NF-κB signaling, and reducing pro-fibrotic mediators, quercetin protects renal tissue from structural and functional damage [33]. Its vasodilatory properties also improve renal perfusion, contributing to hemodynamic protection [32].

Berberine, an isoquinoline alkaloid from Berberis species, exerts nephroprotective effects via antioxidant and anti-inflammatory mechanisms, regulation of lipid and glucose metabolism, and inhibition of fibrotic signaling [34]. In diabetic rodent models, berberine reduces proteinuria, preserves glomerular architecture, and decreases tubular apoptosis [33].

In addition to individual phytochemicals, traditional formulations from Ayurvedic, Chinese, and African medicine are frequently employed for kidney protection. Examples include Punarnava extracts in Ayurveda and Chinese multi-herb decoctions like Shenqi Wan [35,36]. While preclinical studies often show efficacy, variability in composition, dosing, and preparation limits reproducibility and clinical translation.

Overall, these representative herbal candidates demonstrate the potential of phytochemicals to prevent or attenuate nephrotoxicity through multi-faceted mechanisms. Their efficacy is context-dependent, influenced by dose, formulation, pharmacokinetics, and underlying renal pathology. Continued research on standardized preparations and clinical validation is essential to fully harness their nephroprotective potential.

CONCLUSION

Nephrotoxicity is a global health burden driven by drugs, toxins, and metabolic disorders. Herbal medicines present a dual narrative: they can mitigate renal injury through antioxidant, anti-inflammatory, mitochondrial, and antifibrotic mechanisms, yet also pose nephrotoxic risks due to intrinsic toxicity, contamination, or interactions. The challenge is to harness their protective potential while safeguarding against harm. This requires standardized formulations, mechanistic insights, and high-quality clinical trials. With appropriate safeguards, phytomedicines could evolve from traditional remedies into scientifically validated adjuncts in nephroprotection.

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