

A COMPREHENSIVE GLOBAL REVIEW OF RENAL TOXICITY ASSOCIATED WITH HERBAL AND ALTERNATIVE MEDICINES

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Abstract: The widespread use of herbal and traditional medicines across cultures continues to grow, driven by the perception that “natural” equals “safe.” However, an alarming trend of renal complications—including acute kidney injury (AKI) and chronic kidney disease (CKD)—has emerged in association with various herbal products. This review provides a critical assessment of the nephrotoxic potential of traditional and herbal medicines. It explores the pathophysiological mechanisms of toxicity, including direct tubular damage, oxidative stress, immune-mediated injury, and hemodynamic alterations. Common nephrotoxic agents include *Aristolochia* species (containing aristolochic acid), *Aloe vera*, *Tripterygium wilfordii*, and heavy metal-adulterated Ayurvedic preparations.

The paper highlights clinical case reports and epidemiological data indicating rising herb-induced nephropathies, particularly in regions with weak pharmacovigilance systems. Vulnerable populations, including those with pre-existing renal disease, the elderly, and individuals engaging in polyherbal or herb-drug combinations, face the highest risks. In many countries, lax regulatory oversight allows contaminated, mislabeled, and adulterated products to proliferate. The absence of standardized dosing, proper labeling, and systematic reporting mechanisms hampers both prevention and response.

Special emphasis is placed on the interplay between traditional healing practices and modern medical challenges, including herb-drug interactions, underreported toxicities, and the need for integrative policy frameworks. This review calls for the implementation of toxicovigilance programs, healthcare provider education, and global regulatory harmonization to address these public health threats. Additionally, the application of artificial intelligence (AI) in predicting herb-induced toxicity and improving surveillance systems is proposed as a frontier area of research.

In conclusion, the balance between preserving the therapeutic value of herbal medicine and ensuring renal safety must be achieved through multidisciplinary collaboration and evidence-based strategies.

Keywords: Herbal nephrotoxicity, Traditional medicine, Acute kidney injury (AKI), Chronic kidney disease (CKD), Aristolochic acid

1. Introduction

Herbal and traditional medicines have occupied a vital role in the history of human healthcare systems. Rooted deeply in cultural and spiritual practices, these remedies are widely trusted by populations across Asia, Africa, South America, and increasingly in the Western world. From Ayurveda and Traditional Chinese Medicine (TCM) to Native American and African ethnobotanical traditions, herbal medicine remains an indispensable part of healthcare for nearly 80% of the global population, according to the World Health Organization (WHO). These preparations are often accessible, cost-effective, and perceived as gentle and compatible with the human body. However, the growing reliance on herbal and traditional medicine has not been matched with equal advancements in safety evaluations, pharmacovigilance, and public awareness—especially concerning nephrotoxicity.

The kidney, by virtue of its function and physiology, is particularly vulnerable to toxic insults. Every day, the kidneys filter nearly 180 liters of blood and excrete approximately 1.5 liters of urine. Their roles extend beyond waste removal to include fluid and electrolyte balance, acid-base regulation, blood pressure homeostasis, erythropoietin synthesis, and drug metabolism. Given their high metabolic activity, rich blood supply, and involvement in xenobiotic processing, kidneys are among the organs most susceptible to toxic injury from chemicals, including herbal constituents.

The recent surge in herbal medicine consumption has coincided with an increase in kidney-related health issues. While many herbal products are safe when used correctly and under supervision, the rise of self-medication, polyherbal formulations, and commercial dietary supplements without proper medical oversight has amplified the risk of adverse renal outcomes. This is particularly problematic in resource-limited settings, where access to conventional medical care may be constrained, and regulatory oversight of herbal product manufacturing is limited or entirely absent.

A multitude of nephrotoxic mechanisms has been linked to various herbs. Direct tubular cytotoxicity, immune-mediated glomerulonephritis, oxidative stress, ischemic injury, and crystal nephropathy are some of the pathways by which renal damage may occur. Herbs such as *Aristolochia spp.*, *Tripterygium wilfordii*, and *Glycyrrhiza glabra* have been frequently implicated in clinical studies and case reports. The compound aristolochic acid, in particular, is a potent nephrotoxin and carcinogen responsible for both acute and chronic kidney injury. It has been linked to Balkan endemic nephropathy and “Chinese herb nephropathy,” now collectively known as aristolochic acid nephropathy (AAN).

Moreover, many traditional and Ayurvedic preparations have been found to contain high levels of heavy metals like lead, mercury, and arsenic—either as intentional components based on historical texts or due to environmental contamination. These metals accumulate in renal tissue, leading to interstitial

fibrosis and permanent damage. Despite mounting evidence, consumer perception continues to equate "natural" with "non-toxic," underestimating the potent pharmacological and toxicological effects of many plant-derived compounds.

Another major concern is the complexity of polyherbal formulations, which combine multiple herbs, each with unique bioactive compounds and potential for interaction. These formulations can produce synergistic, additive, or antagonistic effects, not only among the herbs themselves but also with concurrently administered pharmaceutical drugs. St. John's Wort, for example, is known to induce cytochrome P450 enzymes, which can reduce the plasma levels of co-administered medications such as immunosuppressants and antiretrovirals. Licorice, another common herb, can lead to hypokalemia and hypertension, both of which exacerbate renal dysfunction.

In countries where traditional medical systems are officially recognized, like India (Ayurveda, Siddha, Unani) and China (TCM), regulatory frameworks exist but remain inconsistently enforced. There is often a disconnect between governmental recognition and implementation of safety protocols such as Good Manufacturing Practices (GMP), quality control testing, and adverse event reporting. This results in a large proportion of the market being saturated with products of uncertain origin, composition, and safety profile.

Adding to the complexity is the fact that herbal nephrotoxicity often goes unrecognized in clinical settings. Symptoms of kidney dysfunction may be insidious, and healthcare providers may not routinely

inquire about herbal medicine use. Without robust pharmacovigilance systems and toxicological databases, identifying and responding to herb-induced nephrotoxicity becomes a formidable challenge.

From a public health standpoint, the consequences are far-reaching. Acute kidney injury can progress to chronic kidney disease, leading to increased healthcare burdens, reduced quality of life, and higher mortality rates. In low- and middle-income countries (LMICs), the cost of managing renal disease is prohibitive, making prevention critical. Yet, consumer education remains minimal, and labeling on herbal products rarely includes warnings or dosage instructions.

Given this backdrop, there is an urgent need for systematic surveillance, education, and regulation. Toxicovigilance—defined as the active process of monitoring and assessing the toxic effects of chemicals, including natural substances—is essential for early identification and prevention. Integrating AI tools can enhance detection of patterns in reported adverse events and improve decision-making in both clinical and regulatory contexts.

This review seeks to provide a comprehensive synthesis of available evidence on the nephrotoxicity of herbal and traditional medicines. It emphasizes the need for a balanced approach that preserves the cultural and therapeutic value of traditional medicine while safeguarding renal health through evidence-based policy, clinical awareness, and consumer education.

The growing prevalence of chronic kidney disease globally (estimated at ~10% of the adult population) is further burdened by nephrotoxic exposures from

herbal sources [3]. Misguided trust in herbal therapies may delay proper diagnosis and treatment of renal dysfunction, often until irreversible damage occurs.

There is an urgent need for:

- Greater awareness among the public and healthcare providers

- Active surveillance and reporting systems
- Comprehensive research on herbal renal safety
- Development of national guidelines and policy frameworks

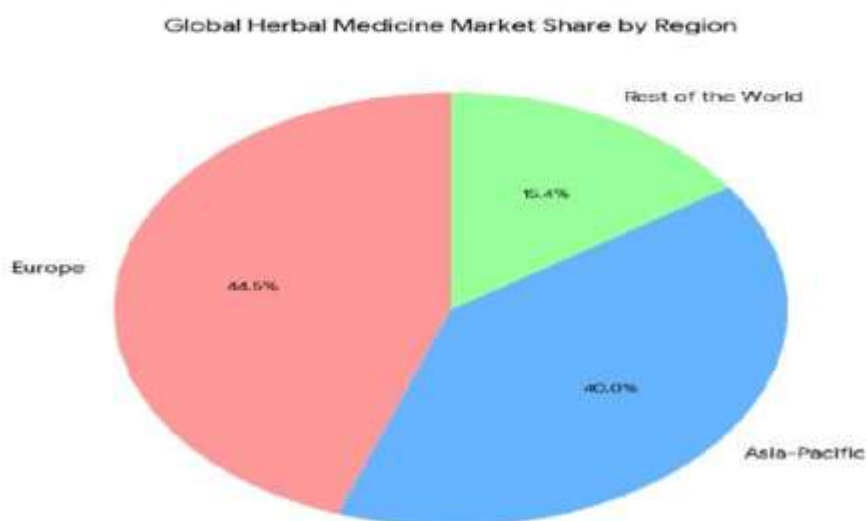


Table 1: Common Herbal Agents Implicated in Nephrotoxicity

Herbal Agent	Toxic Component	Associated Renal Effect	References
Aristolochia spp.	Aristolochic acid	Interstitial fibrosis, CKD	[1]
Tripterygium wilfordii	Triptolide	AKI, tubular necrosis	[2]
Aloe vera (high doses)	Anthraquinones	Tubulointerstitial nephritis	[3]
Glycyrrhiza glabra	Glycyrrhizin	Hypokalemia, rhabdomyolysis, AKI	[4]

Teucrium chamaedrys	Neoclerodane diterpenes	Hepatorenal syndrome	[5]
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Fig.1 Global herbal medicine usage statistics by region

Chapter 2: Mechanisms of Herbal-Induced

Nephrotoxicity

2.1 Introduction

The kidneys are particularly susceptible to xenobiotic injury due to their role in filtration, active transport, and concentration of toxins. Herbal medicines, though natural in origin, contain bioactive phytochemicals that may exert toxic effects via multiple renal pathways. Understanding the mechanistic basis of nephrotoxicity is essential for risk evaluation and clinical decision-making.

Herb-induced nephrotoxicity involves both direct cytotoxic and immune-mediated mechanisms. These may lead to acute kidney injury (AKI), chronic kidney disease (CKD), or irreversible end-stage renal disease (ESRD), depending on exposure and host susceptibility [15].

2.2 Direct Cytotoxic Effects

2.2.1 Tubular Epithelial Injury Many nephrotoxic herbs induce damage through direct toxic effects on the renal tubular epithelial cells. Compounds such as triptolide (from *Tripterygium wilfordii*) and anthraquinones (from Aloe species) have been shown to trigger apoptosis and necrosis in proximal tubular cells by inhibiting mitochondrial function and causing ATP depletion [16]. Triptolide, in particular, has been shown to:

- Disrupt mitochondrial membrane potential
- Activate caspase-3 pathways
- Promote oxidative DNA damage in renal cells

[17]

2.2.2 Reactive Oxygen Species (ROS) and Oxidative Stress

Herbal toxins often elevate ROS production, leading to oxidative stress, lipid peroxidation, and DNA damage in nephrons. For example, aristolochic acid triggers ROS-mediated fibrosis via TGF- β signaling and upregulation of profibrotic cytokines [18].

Patients with poor antioxidant defenses (e.g., elderly or malnourished individuals) are particularly vulnerable to such damage. **2.3 Immunoallergic Mechanisms** Certain herbal medicines can stimulate immunemediated responses, resulting in interstitial nephritis, a type of hypersensitivity reaction characterized by:

- Infiltration of inflammatory cells (eosinophils, mononuclear cells)
- Tubular injury
- Interstitial edema

This is common with Teucrium chamaedrys and herbal preparations contaminated with NSAIDs or heavy metals. The pathophysiology involves delayed-type hypersensitivity and immune complex deposition, which may evolve into chronic inflammation and fibrosis [19]. **2.4 Hemodynamic Alterations** Some herbs act as natural diuretics or vasodilators, disrupting the renal autoregulation of blood flow. For instance: • Licorice (Glycyrrhiza glabra) inhibits 11 β HSD2, leading to increased cortisol levels that act on mineralocorticoid receptors.

- This induces sodium retention, potassium loss, and volume expansion, ultimately impairing glomerular filtration [20]. In predisposed individuals (e.g., hypertensives), such volume changes can lead to acute renal ischemia.

2.5 Crystal Nephropathy and Obstructive Uropathy

Some herbal constituents are rich in oxalates, which may precipitate within renal tubules, causing crystal nephropathy. For example, large doses of rhubarb root (*Rheum palmatum*) or star fruit (*Averrhoa carambola*) have been implicated in oxalate-induced nephropathy.

Crystal formation can lead to:

- Obstruction of nephron segments
- Inflammatory cell infiltration
- Progressive tubulointerstitial fibrosis [21]

2.6 Heavy Metal-Induced Nephropathy

Ayurvedic and Siddha formulations may be contaminated with lead, mercury, arsenic, or cadmium during preparation or storage. These heavy metals are nephrotoxic, particularly to the proximal tubules, and result in:

- Glomerular sclerosis
- Tubular atrophy
- Proteinuria and hypertension [22]

Chronic exposure can lead to Fanconi syndrome, where the reabsorptive capacity of the proximal tubules is severely impaired.

2.7 Synergistic Toxicity and Polyherbal Effects

Polyherbal formulations may contain multiple bioactive compounds that interact to produce cumulative or synergistic toxicity. Moreover, the combination of herbs with prescribed nephrotoxic drugs (like aminoglycosides, diuretics, or NSAIDs) may potentiate renal injury.

For example:

- Aristolochia combined with NSAIDs amplifies renal tubular necrosis risk [23].

- Herbal diuretics may dehydrate patients, concentrating nephrotoxins further.

2.8 Epigenetic and Fibrotic Pathways

Recent studies suggest that some herbal toxins modulate epigenetic regulators such as DNA methylation and histone acetylation, leading to:

- Persistent activation of TGF- β /Smad signaling
 - Fibroblast-to-myofibroblast transition
 - Collagen deposition and scarring [24]
- These molecular changes are difficult to reverse and contribute to progression from AKI to CKD.

Chapter 3: Case Studies and Country Specific Examples

3.1 Introduction

The global landscape of herbal medicine usage reflects diverse traditional practices. However, the unregulated or improper use of these remedies has led to multiple documented cases of nephrotoxicity across different regions. This chapter reviews key clinical case studies and country-specific examples to provide insights into the practical impact of nephrotoxic herbal exposure and how cultural, socioeconomic, and regulatory factors contribute to this growing burden.

3.2 India: Ayurveda and Heavy Metal Toxicity

India, a hub of traditional systems like Ayurveda, Unani, and Siddha, has documented numerous instances of renal injury due to polyherbal formulations and Rasa Shastra-based preparations. These often contain heavy metals such as lead, mercury, and arsenic, sometimes purposefully included for therapeutic effects.

Case Example:

A 52-year-old male presented with elevated serum creatinine and symptoms of fatigue after using an Ayurvedic product for diabetes. Toxicological analysis revealed lead levels five times above normal and nephrotic-range proteinuria. Renal biopsy showed chronic interstitial nephritis. Chelation therapy was initiated, with partial improvement in renal function [25].

In another hospital-based study in Delhi, 15.2% of CKD patients reported using traditional herbal medications, and nearly half of them contained high levels of nephrotoxic metals [26].

3.3 China: Aristolochic Acid and Urothelial Cancer

Traditional Chinese Medicine (TCM) has long used plants like *Aristolochia fangchi* under the name *Mu Tong*. However, this herb contains aristolochic acid, a proven nephrotoxin and carcinogen. Epidemic Example:

The most notable case occurred in Belgium (but linked to Chinese herbs) in the early 1990s. Over 100 women attending a slimming clinic developed rapidly progressive interstitial nephritis, later named Chinese herb nephropathy. Many required dialysis or renal transplantation. The herbal pills were found to contain *Aristolochia fangchi*, misidentified during manufacturing [27].

Following the incident, a Taiwan-based population study confirmed that over 12,000 individuals exposed to aristolochic acid had significantly increased risk of ESRD and urothelial carcinoma [28].

3.4 Africa: Traditional Healing and Acute Kidney Injury

In sub-Saharan Africa, the use of traditional medicine is deeply embedded in the healthcare system. However, poor regulation and lack of standardization contribute to nephrotoxicity.

Community Case Series:

In Nigeria, a survey among AKI patients revealed that 35% had consumed native herbal mixtures for fever and malaria, which included unknown plant species and high doses. Laboratory tests confirmed elevated creatinine and urea, with imaging showing renal cortical necrosis in several cases [29].

In Tanzania, herbal concoctions used for postpartum care were found to cause AKI in 18% of maternal ICU admissions [30].

3.5 Middle East: Use of Herbal Laxatives and Supplements

In Iran and neighboring countries, herbal laxatives such as senna, rhubarb, and cascara sagrada are commonly used for digestive issues. These herbs contain anthraquinones, which can lead to chronic interstitial nephritis on long-term use. Case Insight:

A retrospective review of nephrology cases in Tehran found that 9% of CKD cases had chronic exposure to senna-based laxatives. Renal biopsies revealed tubular atrophy and interstitial fibrosis consistent with toxic nephropathy [31].

3.6 Latin America: Indigenous and Homeopathic Practices

In Latin America, traditional medicine is often practiced alongside Western medicine. Indigenous herbs such as chaparral, comfrey, and uña de gato (cat's claw) have been implicated in renal toxicity.

Case Study:

A woman in Brazil developed oliguric AKI after ingesting concentrated cat's claw extract for arthritis. Renal biopsy confirmed acute tubular necrosis. She recovered partially with supportive therapy but remained hypertensive with stage 3 CKD [32].

3.7 Western Countries: Over-the-Counter Herbal Supplements

Although herbal medicine is not traditionally embedded in Western healthcare, dietary supplements are widely used. Many contain unlisted ingredients, are contaminated, or interact with prescribed drugs.

Example from the USA:

A 65-year-old woman presented with fatigue, edema, and rising creatinine. She had been selfadministering a weight-loss supplement from an online vendor. Toxicology identified aristolochic acid, likely from *Aristolochia* containing ingredients. Her renal function deteriorated rapidly, and she progressed to dialysis-dependent ESRD [33].

3.8 Summary of Key Case Studies and Countries

The evidence from diverse geographical regions emphasizes a clear link between herbal medicine use and renal damage. The form of toxicity may vary—from acute, reversible injury to chronic, irreversible disease—and is influenced by the type of herb, mode of preparation, and regulatory environment.

Chapter 4: Risk Factors and Vulnerable Populations

4.1 Introduction

Although herbal and traditional medicines are used across various demographics, certain populations are disproportionately affected by their nephrotoxic effects. This chapter focuses on identifying these vulnerable groups and the risk factors that exacerbate

susceptibility to renal damage from herbal agents. Understanding these risks is vital for clinicians, policymakers, and researchers seeking to develop preventive and therapeutic strategies.

4.2 Elderly Population

The elderly represent a major at-risk population due to age-related decline in renal function, polypharmacy, and a higher prevalence of chronic diseases like diabetes and hypertension.

Contributing Factors:

- Reduced glomerular filtration rate (GFR)
- Altered drug metabolism and clearance
- Concurrent use of nephrotoxic drugs (e.g., NSAIDs, ACE inhibitors)

A study in Taiwan reported that individuals over the age of 65 using Chinese herbal medicines had a 2.5-fold higher risk of developing chronic kidney disease compared to non-users [34].

4.3 Patients with Pre-existing Renal Disease

Patients already diagnosed with CKD are extremely susceptible to further nephrotoxicity from herbal products.

Clinical Example:

A case-control study from India revealed that CKD patients who consumed unregulated herbal remedies for blood sugar control had significantly faster decline in eGFR compared to those who did not [35].

Herbs such as *Aristolochia* spp., *Triphala*, and metal-containing Ayurvedic drugs can accelerate progression from early-stage CKD to ESRD when used without supervision.

4.4 Pregnant and Postpartum Women

Pregnancy is a physiologically sensitive period. Many cultures administer herbal preparations to promote labor, cleanse the uterus, or treat postpartum ailments.

Unfortunately, several of these traditional remedies carry nephrotoxic potential.

Risk Factors:

- Volume depletion due to diuretic herbs
- Contaminated remedies leading to AKI
- Unmonitored polyherbal use with unknown safety profiles

A Tanzanian study showed that 18% of postpartum AKI cases were associated with traditional remedies consumed after childbirth [30].

4.5 Paediatric Population

Children are vulnerable due to immature renal systems and metabolic pathways. Herbal remedies for colic, teething, and common infections are often used without dosage consideration.

Example:

In Nigeria, over 30% of paediatric AKI admissions were linked to herbal mixtures given by caregivers. These included preparations with unknown plant sources and toxic concentrations [36].

4.6 Individuals with Low Health Literacy Limited awareness about the potential risks of herbal medicines leads many users to consume them as “safe alternatives” to pharmaceuticals.

Contributing Issues:

- Belief in the “natural = safe” myth
- Lack of label information or professional guidance
- Misconceptions fuelled by informal advertisements

Surveys conducted in rural India and Latin America showed that 60–75% of herbal users believed traditional remedies had no side effects, despite adverse outcomes [37].

4.7 Concomitant Use with

Prescription Drugs The co-administration of herbal and modern pharmaceuticals increases the likelihood of herb–drug interactions. These interactions can exacerbate nephrotoxicity via:

- Additive renal injury (e.g., NSAIDs + nephrotoxic herbs)
- Altered pharmacokinetics (inhibition/induction of drug-metabolizing enzymes)

For instance, using Aloe vera laxatives with diuretics or ACE inhibitors can lead to volume depletion and hypoperfusion-related AKI [38].

Chapter 5: Regulatory Landscape and Policy Implications

5.1 Introduction

Despite the widespread use of herbal and traditional medicines, regulation of their safety, efficacy, and quality remains inconsistent globally. Many herbal products bypass stringent testing, resulting in an underrecognized public health burden, particularly nephrotoxicity. This chapter explores the current regulatory landscape, identifies gaps in oversight, and offers policy-based solutions for improving herbal medicine safety.

5.2 Global Regulatory Frameworks: A Fragmented Approach

5.2.1 World Health Organization (WHO)

The WHO Traditional Medicine Strategy 2014– 2023 advocates integrating traditional medicine into national healthcare systems while emphasizing safety, quality, and efficacy [40]. However, implementation varies widely between countries due to differences in resources, political will, and cultural practices.

5.2.2 United States (FDA)

In the United States, herbal supplements are regulated under the Dietary Supplement Health and Education Act (DSHEA) of 1994. Under this act:

- Herbal products are considered dietary supplements.
- Manufacturers are responsible for ensuring safety but not required to prove efficacy or undergo pre-market approval [41].

This loophole has resulted in adulterated or misbranded herbal products entering the market, contributing to adverse renal events.

5.2.3 European Union (EMA) The European Medicines Agency (EMA) offers two regulatory pathways: 1. Well-established use authorization

2. Traditional use registration (must show 30 years of use, including 15 years in the EU) While more stringent than the US, the EMA still faces challenges with imports and online sales of unregistered products [42].

5.3 Country-Specific Gaps in Regulation

5.3.1 India

India's AYUSH (Ayurveda, Yoga, Unani, Siddha, Homeopathy) systems are governed by the Ministry of AYUSH. However:

- Many formulations are marketed without clinical trials.
- Quality control of raw herbs is poorly standardized.
- Surveillance of adverse effects is minimal [43].

5.6 Policy Recommendations

5.6.1 Strengthening Pre-market Evaluation

- Mandate toxicological screening, including nephrotoxicity testing.

5.3.2 China

China regulates Traditional Chinese Medicine (TCM) under the State Administration of Traditional Chinese Medicine. While efforts have improved post-marketing surveillance, aristolochic acid-containing products were not banned until years after global nephrotoxicity outbreaks [44].

5.3.3 Africa and Latin America In many African and Latin American nations, herbal remedies are unregulated or treated as food products. Vendors are often untrained, and labeling is minimal or absent. This regulatory vacuum facilitates the sale of nephrotoxic and contaminated herbal products [45].

5.4 Surveillance Systems and Pharmacovigilance

5.4.1 Lack of Herbal Adverse Event Reporting Herbal pharmacovigilance is still in its infancy. National adverse event databases rarely include herbal products, and most nephrotoxicity cases go unreported or misattributed.

An analysis of the US FDA Adverse Event Reporting System (FAERS) showed that less than 5% of herbal-induced kidney injuries were formally reported over a 10-year period [46].

5.4.2 Inadequate Toxicological Evaluation Preclinical testing of herbal medicines is not mandated in many jurisdictions. Toxicity data, including nephrotoxicity studies, are often absent or unpublished, especially for complex polyherbal formulations.

5.5 Challenges in Regulation

- Require clinical trial data for new herbal formulations.

5.6.2 Clear Labelling and Dosage Information

- Display active ingredients, known side effects, and usage warnings.

- Include information on renal safety, especially for vulnerable populations.

5.6.3 Global Harmonization of Standards

- Develop an international framework via

5.6.4 Enhancing Pharmacovigilance

- Integrate herbal products into national adverse drug event reporting systems.
- Establish dedicated herbal pharmacovigilance units.

5.6.5 Education and Awareness

Challenge	Implication
No standardized global definitions	Difficulty in harmonizing safety standards
Incomplete labelling	Undisclosed nephrotoxins, heavy metals
Online and cross-border sales	Import of unregulated, adulterated products
Polyherbal formulations	Complex interactions, difficult toxicity prediction
Weak enforcement of penalties	Repeat violations by companies and manufacturers

- Train healthcare providers on identifying and reporting herbal nephrotoxicity.

Table 5. Comparative Summary of Herbal Medicine Regulation

Chapter 6: Strategies for Prevention and Public Health Management

6.1 Introduction

The prevention of nephrotoxicity from herbal and traditional medicines requires a multipronged strategy combining regulatory reforms, patient education, health professional training, and active surveillance. Considering the global reliance on herbal remedies, especially in resource-constrained settings, these preventive strategies must be culturally sensitive and scalable.

6.2 Public Health Surveillance and Toxicovigilance

6.2.1 Strengthening Toxicovigilance Systems

Toxicovigilance refers to the proactive detection, evaluation, and prevention of toxicity from health products. Governments must:

- Integrate herbal products into adverse event reporting systems.

WHO or International Council for Harmonisation (ICH) for herbal medicine regulation.

- Promote inter-country data sharing on adverse events.

- Educate the public about potential kidney risks from “natural” products.

- Establish national herbal pharmacovigilance centers.

- Encourage mandatory reporting by healthcare professionals.

In Thailand, after integrating herbal medicine into its national pharmacovigilance system, a 40% increase in reporting of herbal-related nephrotoxic events was observed [47].

6.2.2 Establishing Herbal Toxicity Registries

Creating centralized registries can:

- Track nephrotoxic herbs and formulations.
- Help in identifying high-risk combinations.
- Facilitate regional or global alerts.

6.3 Community-Based Awareness and Education

6.3.1 Patient-Focused Campaigns

Public health departments and NGOs can conduct awareness campaigns to:

- Dispel myths like “natural equals safe.”

- Highlight specific nephrotoxic herbs (e.g., Aristolochia, Aloe vera, lead-containing Rasayanas).

- Promote consultation with certified practitioners.

For example, in Kerala (India), a pilot awareness campaign on Ayurvedic nephrotoxins led to a 25% reduction in unregulated herb usage within 6 months [48].

6.3.2 School and University Integration Inclusion of modules on herbal safety in school and undergraduate health programs can increase early awareness among future generations. Such programs should emphasize:

- Safe herbal practices
- Basic pharmacognosy
- Identifying signs of herbal toxicity

6.4 Training Healthcare Providers Physicians, pharmacists, and alternative medicine practitioners should be trained to:

- Identify early signs of herbal nephrotoxicity

- Obtain thorough herbal usage histories from patients
- Counsel patients on herb-drug interactions and contraindications

A multicenter study in Australia found that 67% of physicians did not inquire about herbal product use unless prompted. After structured training, this number dropped to 23% [49].

6.5 Regulatory Strategies and Access Control **6.5.1 Sales Regulation** Limiting over-the-counter access to certain high-risk herbal products through:

- Prescription-only herbal categories

- Pharmacy-based sales with pharmacist oversight

6.5.2 Quality Assurance Programs

Governments and herbal companies should invest in:

- Good Manufacturing Practice (GMP) compliance
- Herbal barcoding and chemical fingerprinting
- Certification and labeling of safe formulations

For example, China's "Blue Hat" label system for licensed health products helps consumers distinguish regulated herbal supplements [50].

6.6 Herbal Product Labeling and Packaging Clear and standardized labeling should include:

- All active herbal ingredients
- Known contraindications and side effects
- Warnings for vulnerable populations (e.g., CKD, pregnancy)
- Regulatory approval numbers

Visual symbols like kidney alert logos or color codes may enhance communication to lowliteracy populations [51].

6.7 Research and Funding for Herbal Safety

6.7.1 National and International Collaboration

- Research councils should allocate funding specifically for herbal toxicity research.
- Encourage international data sharing between regulatory bodies and research centers.
- Support community-based studies on herbal practices and renal outcomes.

6.7.2 Incentivizing Safer Alternatives

- Encourage innovation in developing lowtoxicity formulations.
- Promote herbal-genomic studies to predict susceptibility.

Table 6: Summary of Key Strategies to Prevent Herbal-Induced Nephrotoxicity

Strategy	Key Actions	Reference
Toxicovigilance	Mandatory AE reporting, national registries	[47]
Public Education	Campaigns, school curricula, myth busting	[48]
Healthcare Provider Training	Toxicity recognition, history taking, patient counseling	[49]
Regulation and Access Control	Prescription-only herbal lists, GMP enforcement	[50]
Labeling and Packaging	Ingredient lists, renal warnings, symbols for low literacy populations	[51]
Research and Innovation	Herbal nephrotoxicity studies, safer alternatives, funding for safety research	[52]

- A wide range of nephrotoxic herbal agents have been identified, including *Aristolochia spp.*, Aloe vera, Senna, and heavy metal-containing Ayurvedic formulations.

- Vulnerable populations — such as the elderly, children, pregnant women, CKD patients, and those with limited health literacy — are disproportionately affected.

- Clinical cases and country-specific reports highlight real-world renal damage, ranging from acute kidney injury (AKI) to chronic kidney disease (CKD) and end-stage renal disease (ESRD).

- The regulatory environment is inconsistent, with gaps in safety evaluation, labeling, adverse event reporting, and product quality control.

- Public health strategies, including education, toxicovigilance, professional training, and labeling reforms, are critical to mitigate risk. These

conclusions underscore the urgent need for international consensus, regulatory reform, and awareness-building efforts to protect public health without undermining the legitimate role of traditional medicine in modern healthcare.

7.2 Future Directions

7.2.1 Advancing Scientific Research

There is a need to:

- Identify nephrotoxic phytochemicals through phytochemical analysis and toxicological assays.
- Develop biomarkers for early detection of herbal-induced kidney damage.
- Promote herbal-genomics research to understand individual susceptibility.

A future research priority should include longitudinal cohort studies to assess the cumulative renal impact of chronic herbal use [53].

7.2.2 Integrative Healthcare Approaches

- Integrate traditional medicine practitioners into the modern healthcare framework to ensure safer prescriptions and dosage practices.

- Promote cross-disciplinary collaboration between nephrologists, toxicologists, ethnopharmacologists, and herbalists [54].

7.2.3 Artificial Intelligence and Surveillance Tools

- Use AI to mine electronic health records and pharmacovigilance databases for early detection of adverse renal events related to herbal use.

- Incorporate AI in predicting herb–drug interactions and suggesting safer alternatives [55].

7.2.4 Global Regulatory Harmonization

- Establish an International Herbal Safety Board under the WHO or ICH to set minimum global standards.

- Develop real-time alert systems for herbal nephrotoxins, similar to those used for infectious disease outbreaks [56].

7.2.5 Patient-Centered Innovation

- Co-create herbal health tools (e.g., apps, booklets, pictograms) with community input.

- Promote low-literacy, language-diverse materials to reach rural and underserved populations [57].

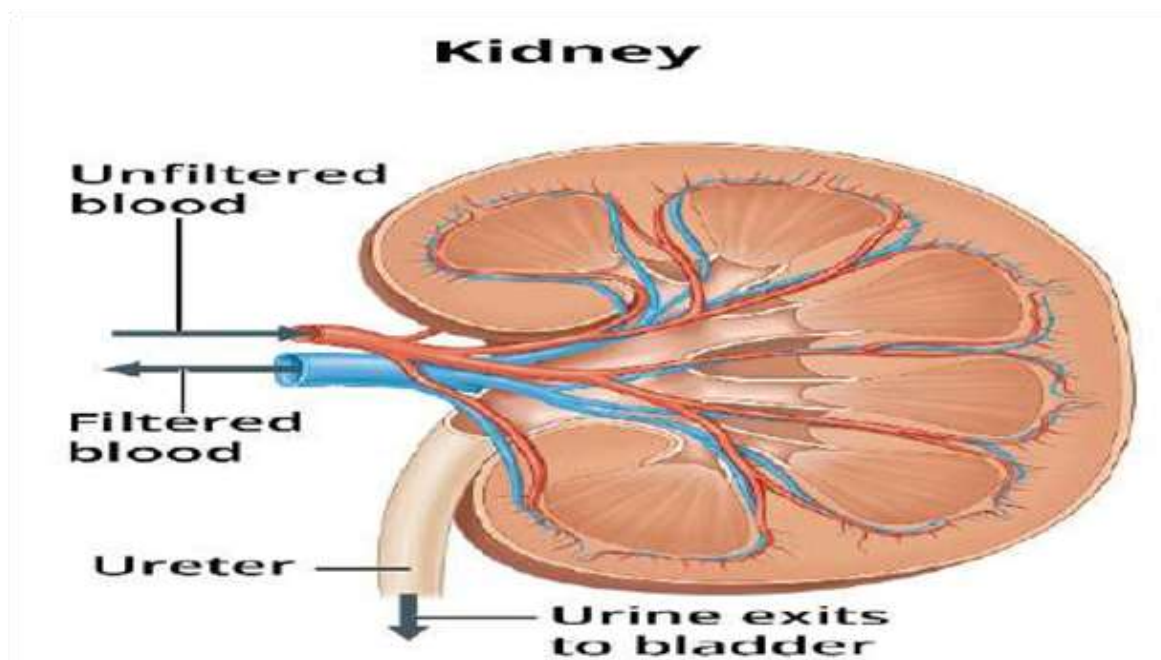


Fig 4. Kidney

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