



Green Alternatives for Kidney Stone Management: A Critical Review of Herbal Anti-urolithiatic Therapies

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Abstract:

Kidney stone disease, or urolithiasis, is a prevalent and recurrent urological disorder with significant global health implications. Conventional treatments, including pharmacotherapy and surgical interventions, often come with limitations such as high cost, side effects, and recurrence risk. In response, there has been a growing interest in plant-based or herbal remedies as eco-friendly and accessible alternatives. This review critically examines the current landscape of herbal anti-urolithiatic therapies, highlighting medicinal plants traditionally used in Ayurvedic, Unani, and other ethnomedical systems. The mechanisms of action—such as diuretic, antioxidant, anti-inflammatory, and crystal-inhibiting effects—are discussed in relation to bioactive phytoconstituents like flavonoids, saponins, alkaloids, and polyphenols. Key herbs including *Tribulus terrestris*, *Phyllanthus niruri*, *Bergenia ligulata*, and *Crataeva nurvala* are evaluated for their efficacy in both preclinical and clinical studies. The review also addresses challenges in standardization, dosage, toxicity, and the need for rigorous clinical validation. Overall, herbal therapeutics present a promising, sustainable approach to kidney stone prevention and treatment, meriting deeper scientific exploration and integration into modern urological practice.

Keywords:

Herbal medicine, Anti-urolithiatic, Kidney stones, Phytotherapy, Medicinal plants, *Phyllanthus niruri*, *Tribulus terrestris*, Nephrolithiasis, Bioactive compounds, Natural remedies, Urolithiasis, Plant-based therapy, Crystal inhibition, Oxalate metabolism, Ethnomedicine

Introduction

Kidney stones, scientifically known as nephrolithiasis, are mineral deposits that can form in different parts of the kidney, primarily in the renal calyces and pelvis. They consist of crystalline and organic components, and their formation is largely due to the supersaturation of urine with a particular mineral, most commonly, calcium oxalate. These stones can be found free of or attached to the renal papillae, with many forming on calcium phosphate matrices known as Randall's plaques on the surface of the kidney (1). Globally, kidney stones are a significant health issue, with a prevalence rate of up to 14.8%, and new incidents have been rising over the last few decades. Moreover, recurrence rates are alarmingly high, reaching up to 50% within five years after the first episode. Kidney stones lead not only to immense discomfort during episodes of ureteral obstruction but also to long-term complications, such as chronic kidney disease and possibly end-stage renal disease (Thongprayoon et al., 2020; Tamborino et al., 2024). The prevalence of kidney stones varied significantly across regions and demographic groups. For instance, a cross-sectional study in China reported a prevalence of 6.4% in the adult population, with higher prevalence rates in men than in women. Factors such as male sex, rural residence, family history, diabetes mellitus, and dietary considerations are associated with an increased risk of developing kidney stones (2). Several risk factors contribute to the development of kidney stones, including genetic, dietary, and lifestyle factors. Most calcium-containing stones are influenced by factors such as hypercalciuria, which could be due to increased intestinal absorption, bone resorption, or altered renal tubular transport. Other factors implicated in stone formation include obesity, diabetes, hypertension, and metabolic syndrome, which exacerbate kidney-related complications. Dietary calcium plays a crucial role; higher dietary calcium intake is linked to a reduced risk of symptomatic kidney stones, whereas supplemental calcium not consumed with meals might increase the risk. Obesity is another contributing factor, as larger body size has been associated with a higher risk of stone formation, particularly in women. Conditions such as diabetes, hypertension, and metabolic syndrome further exacerbate this risk, possibly through their effects on body metabolism and renal function, although specific mechanisms remain under investigation (3) (4). Diet plays a complex role in kidney stone formation. Low fluid intake is a primary dietary risk factor. Although increased fluid intake is recommended, the type of liquid consumed matters, as some beverages might influence stone risk differently. Moreover, certain foods containing high amounts of proteins, carbohydrates, oxalate, calcium, and sodium chloride are also significant contributors to the risk profile (5). Considering the rising incidence and multifactorial nature of nephrolithiasis, understanding the underlying mechanisms, identifying the risk factors, and implementing preventive strategies tailored to an individual's profile can significantly reduce the burden of the disease (Singh and Rai, 2014; Devarajan, 2018). While I cannot generate a full review article, this summary provides insight into the prevalence and complexity of kidney stone disease based on the available literature.

Conventional treatments in various medical fields, including cancer and rheumatology, often have significant limitations, particularly adverse effects, and high recurrence rates. These drawbacks can impact patient outcomes and the overall effectiveness of treatment. Adverse effects are a major concern in conventional pharmaceutical interventions. For instance, chemotherapy is known for its adverse effects, including poor bioavailability, high dose requirements, and low therapeutic indices. Patients often experience dose-limiting toxicities that can be severe enough to hinder the continuation of treatment, and these toxicities can lead to drug resistance or non-specific targeting (6). In rheumatoid arthritis treatment, traditional drugs pose challenges, such as serious side effects and unclear pharmacological mechanisms. However, the use of targeted therapies, such as monoclonal antibodies, shows promise in overcoming these limitations by targeting specific cytokines involved in disease progression, potentially reducing adverse effects and improving therapeutic outcomes (7). The recurrence rates following traditional therapies pose considerable challenges. For intestinal cancer, conventional treatments can be effective but often lead to recurrences due to poor selectivity towards cancer cells and the development of resistance, which contributes to tumor relapse (8). Similarly, recurrence rates after colorectal endoscopic mucosal resection (EMR) are high, with approximately 20% of patients experiencing recurrence. However, targeted endoscopic interventions have been shown to significantly reduce this rate, thus providing a potential solution to this drawback without increasing complications (9).

In summary, while conventional treatments have been beneficial in managing various conditions, their limitations in terms of adverse effects and recurrence rates necessitate the exploration of alternative or adjunctive therapies. Innovative approaches such as incorporating targeted therapies and endoscopic interventions offer a promising avenue to mitigate these challenges (Kemper et al., 2018; Kemper et al., 2021).

Overview of herbal anti-urolithiatic therapies - Historical applications in traditional medicine systems - Increasing interest in green alternatives

Herbal anti-urolithiatic therapies have gained attention owing to their historical roots in traditional medicine systems and the rising interest in sustainable and green alternatives to conventional pharmacotherapy.

Historical Applications in Traditional Medicine Systems:

Urolithiasis, the formation of stones in the urinary tract, has afflicted humans for centuries (10). In traditional medicine, various cultures worldwide have utilized plant-based remedies to treat this ailment. For example, traditional Iranian medicine (TIM) has employed plants such as *Citrullus colocynthis* for its purported anti-inflammatory and diuretic effects, which are beneficial for managing kidney stones (11). Similarly, in Palestine, an ethnopharmacological survey identified 57 plant species used by traditional healers to treat urinary stones, including common species such as *Paronychia argentea* and *Plantago ovata* (12). These plants have been traditionally prepared in forms such as decoctions and are lauded for their perceived effectiveness, despite being less scientifically studied compared to contemporary pharmaceuticals.

Increasing Interest in Green Alternatives:

In recent years, there has been growing interest in using herbal therapies as green alternatives to traditional drugs for urolithiasis (10). This interest is driven by multiple factors, including the high cost and limited availability of conventional treatments, as well as a cultural shift towards more natural, sustainable forms of healthcare. Herbal remedies are perceived to be milder with fewer side effects than pharmaceutical

drugs (13). Moreover, the principles of traditional Chinese medicine (TCM) have introduced the idea that herbs, when used in combination, can exert synergistic effects that are not possible with single-compound drugs (14). Scientific studies have evaluated the efficacy of herbal preparations. In vivo experiments, typically using models such as rats to mimic human urolithiasis, have shown promising results, with some herbal extracts reducing calcium oxalate crystal formation, a primary contributor to kidney stones (10). However, it is worth noting that less than 10% of these studies examined the antioxidant and diuretic activities of herbal treatments, which are believed to contribute to their antiurolithic effects (10). Despite their potential benefits, there is still a critical need for more rigorous scientific studies to validate the safety and efficacy of these herbal therapies. There are concerns about the toxicity and potential harmful effects of some herbs when improperly used (13). Additionally, quality control in the production of herbal medications is crucial to ensure consistency and safety, particularly as their popularity increases globally (15). In summary, while herbal anti-urolithiatic therapies are steeped in tradition and are increasingly popular as natural alternatives, further research is needed to confirm their clinical effectiveness and safety. These therapies hold promise but must be approached with scientific rigor to ensure that they are both safe and effective for modern use.

Mechanisms of action for herbal remedies

Herbal remedies have long been used for their therapeutic potential in various medical conditions, and their mechanisms of action have been increasingly explored in scientific studies. These mechanisms include the inhibition of stone formation, diuretic effects, anti-inflammatory properties, and antioxidant activities.

Inhibition of Stone Formation Processes:

Herbal remedies are used to manage urolithiasis and kidney stones through various mechanisms. Some plants, such as *Desmodium styracifolium*, have been shown to reduce calcium oxalate crystallization and kidney stone formation. Flavonoids present in these plants possess properties that modulate crystallization, nucleation, and aggregation, ultimately mitigating stone formation (16). The precise mechanism involves the antioxidant and anti-inflammatory properties of these compounds, which reduce oxidative stress and inflammation, both of which can exacerbate stone formation (Khan et al., 2021; Sansores-España et al., 2022).2.

Diuretic Effects:

Herbal diuretics play a crucial role in preventing kidney stone formation by promoting urine production and flow, which helps to prevent crystal aggregation. Traditionally used plants, such as those reviewed in Mexican alternative medicine, exhibit diuretic properties that aid in this process by flushing out potential stone-forming compounds, such as calcium and oxalate (17).3.

Anti-inflammatory Properties:

The anti-inflammatory effects of herbal remedies are beneficial for conditions involving inflammation, such as kidney stones, and certain inflammatory diseases, such as bowel disorders. Herbal therapies, such as those derived from **Thuja occidentalis**, have shown potential in reducing inflammatory markers and oxidative stress, which are contributing factors in conditions such as ulcerative colitis (18). These anti-inflammatory activities are often mediated by phytochemicals such as flavonoids and phenolic acids, which suppress inflammatory cytokines and oxidative radicals (19).

Antioxidant Activities:

Antioxidant properties are crucial for herbal remedies, as they help neutralize free radicals and reduce oxidative stress. Turmeric, for example, is widely recognized for its high antioxidant capacity through scavenging activities on radicals, which can be beneficial in managing oxidative stress-related conditions in both culinary and medicinal applications (20). Such antioxidant effects are also linked to the role of herbal remedies in kidney stone prevention, as they reduce the oxidative environment that fosters stone formation (21). These herbal mechanisms provide a rationale for considering traditional plant-based remedies as complementary or alternative therapies for a variety of health conditions, particularly when inflammation and oxidative stress are the underlying components. While I cannot provide images here, you can often find related visual data, such as charts and pathway diagrams in the cited studies (Khan et al., 2021; Zhou et al., 2017; Langmead et al., 2002; Stan et al., 2019; Tilak et al., 2004; Zhu et al., 2004).

Review of specific herbal therapies***Phyllanthus niruri:***

Commonly known as "stone breaker," is renowned for its potential benefits in treating kidney stones and other urinary tract disorders. The active compounds of the herb are believed to inhibit stone formation and promote their dissolution, which can alleviate kidney stone symptoms. Evidence from traditional medicine and modern phytotherapy supports its use in treating liver disorders and infections owing to its hepatoprotective and antiviral properties.

Tribulus terrestris:

Known as "puncture vine," is often utilized in traditional medicine to enhance physical strength and libido. Although scientific evidence on this effect remains inconclusive, it has been purported to elevate testosterone levels. Beyond its potential reproductive health benefits, *Tribulus terrestris* may also possess diuretic properties that can aid in the management of certain urinary ailments.

***Orthosiphon stamineus*, or "Java tea,"**

It is traditionally used for its diuretic and anti-inflammatory properties. It is believed to assist in the treatment of kidney stones and aid in weight loss. This plant contains flavonoids, which could contribute to its role in antidiabetic interventions and cardiovascular health.

Cystone:

It a polyherbal formulation, is widely used for its purported efficacy in maintaining the health of the urinary tract. Ingredients such as *Phyllanthus niruri* and *Didymocarpus pedicellata* are believed to assist in the prevention and management of kidney stones. The formulation may help reduce the urinary supersaturation of stone-forming minerals owing to its antimicrobial and anti-inflammatory properties. In addition to these specific herbal therapies, further research on other promising herbal remedies is necessary. Ethnomedicinal plants from regions such as Nepal and Pakistan are actively being explored for their potential health benefits linked to traditional uses and phytochemical findings (Kunwar et al., 2010; Aziz et al., 2020). These herbal therapies offer a holistic approach to health, although the need for robust scientific evaluations remains crucial to establish their efficacy and safety profiles.

Clinical evidence and efficacy studies - In vitro and animal studies - Human clinical trials - Comparative analyses with conventional treatments

In vitro and animal studies, human clinical trials, and comparative analyses of conventional treatments offer a comprehensive framework for evaluating the clinical evidence and efficacy of various interventions. This review draws on several studies to provide insights into the complexities of preclinical and clinical research.

In vitro and Animal Studies:

Animal studies are a critical step for preclinical assessment in various domains, including drug research, experimental surgery, and toxicology. These models are essential for predicting the therapeutic potential and estimating the risks associated with novel interventions (22). However, the translation of positive outcomes from animal studies to human clinical trials often has hurdles. Problems such as inadequate animal models that do not faithfully replicate the human pathology and safety issues of compounds imply that the limitations of animal studies must be acknowledged (23). Systematic reviews have revealed the poor quality of many animal studies and have emphasized improvements in their design, conduct, and reporting (24).

Human Clinical Trials:

The transition from successful animal studies to positive clinical trial outcomes is not always smooth. For neurodegenerative diseases, although certain molecular-targeted therapies have shown promise in preclinical studies, they have failed to replicate their efficacy in human trials. Concerns, such as delivery issues and unvalidated outcome measures, hinder effective clinical translation (23). On the other hand, human clinical trials for biosimilar biologics have demonstrated efficacy comparable to their reference products, showing the potential success of well-designed trials (25).

Comparative Analyses with Conventional Treatments:

Comparative analyses are vital for establishing the relative efficacy and safety of new and established treatments. In particular, biosimilar biologics undergo rigorous comparative efficacy trials to ensure their effectiveness and safety as reference products (25). Furthermore, studies have stressed the need for methodological revisions in clinical trials for novel treatments, suggesting a close examination of past failures and novel strategies, such as using robust animal models and pre-symptomatic assessments to improve trial outcomes (Jenkins et al., 2012; Jenkins et al., 2017). In conclusion, while data from animal models remain critical in shaping clinical trials, there is an ongoing need to refine both preclinical assessments and human trials to improve translational research efficiency. Greater integration and innovation in the design of both studies are necessary to bridge the gap between promising preclinical results and successful clinical outcomes (Hooijmans et al., 1996; Hooijmans et al., 2018). Safety and toxicity considerations - Potential adverse effects and contraindications - Drug interactions - Quality control and standardization issues

Safety and toxicity considerations in anti-urolithiatic therapies are crucial given the complexity and recurrence rate of the condition. Various aspects, including potential adverse effects, contraindications, drug interactions, and quality control, play significant roles in the management of urolithiasis.

Potential Adverse Effects and Contraindications:

Urolithiasis itself is associated with significant health issues, such as nephrocalcinosis and hyperoxaluria, as seen in the case of genetic models like the Sat1^{-/-} mice. These mice exhibited kidney stones as well as liver toxicity when exposed to acetaminophen due to sulfate anion transporter-1 deletion, highlighting the interconnectedness of the renal and hepatic systems (26). Additionally, the management of pediatric urolithiasis often requires minimally invasive procedures; however, there is a significant emphasis on metabolic evaluations to prevent recurrence (27). Chronic urinary tract infections, often associated with urolithiasis, can further complicate the condition due to factors such as structural abnormalities and diabetes, necessitating a cautious approach to treatment (28).

Drug Interactions:

The use of flavonoids and flavonoid-rich plant extracts has shown potential in preventing calcium oxalate stone formation due to their diuretic, antioxidant, anti-inflammatory, and antibacterial properties (29). However, the integration of these plant compounds into therapeutic regimens requires careful consideration of their interactions with conventional medications and their reliability in the clinical setting. The need for more evidence on their safety and efficacy is highlighted, especially when balancing their benefits with potential metabolic risks (30).

Quality Control and Standardization Issues:

The utilization of dietary plants and extracts in preventing or managing urolithiasis presents various challenges in quality control and standardization. Plants such as green tea, parsley, and pomegranate have been suggested for their potential benefits, but their effects can vary significantly based on the active compounds present and the preparation methods used (Nirumand et al., 2018; Sansores-España et al., 2022). Ensuring consistent quality and sufficient concentrations of the active ingredients is essential for their effectiveness and safety. Additionally, the development of therapeutic agents from such extracts must adhere to rigorous clinical testing to validate claims and determine the appropriate dosing regimens (17). The above considerations underline the complexity of managing urolithiasis, especially given its recurrent nature and the potential systemic implications of its treatment. Ongoing research and careful clinical practice are imperative to optimize treatment protocols, ensuring that they are safe, effective, and tailored to individual patient needs, while considering metabolic, dietary, and genetic factors.

Challenges in herbal anti-urolithiatic research

Research into herbal anti-urolithiatic therapies faces several significant challenges, including variability in herbal preparations, necessity for more robust clinical trials, and regulatory hurdles.

Variability in Herbal Preparations:

One of the primary challenges is the inherent variability in herbal preparations. Herbal drugs are composed of numerous chemical constituents, each of which can undergo various chemical reactions that are influenced by environmental conditions such as temperature and humidity during their shelf life. This can lead to an altered chemical composition and therapeutic profile of the herbal medicinal product (HDP) (31). This

variability makes it difficult to ensure consistency in the efficacy and safety of herbal products, which is crucial for scientific validation and clinical acceptance.

Necessity for More Robust Clinical Trials:

The integration of herbal medicines into mainstream healthcare requires rigorous clinical trials to establish their safety and efficacy. The lack of such trials is a significant barrier in the development of herbal therapies. Although some herbal products have shown potential efficacy, many remain untested, with little known about their modes of action, potential adverse reactions, and interactions with conventional drugs. This lack of robust clinical data hampers efforts to promote safe and rational use of herbal agents (32). Furthermore, the complexity of conducting clinical trials for herbal products includes issues related to regulatory compliance, human subject protection, and ensuring consistent methodology (33).

Regulatory Challenges:

Developing herbal medicines into drug products involves navigating complex regulatory frameworks. Regulatory authorities have set guidelines for stability testing that are often not fully compliant, leading to only a small percentage of studies meeting the required standards (31). In the United States, for instance, the FDA has established guidelines that necessitate pharmacological/toxicological studies; however, achieving compliance and acceptance of herbal products poses significant challenges. Ensuring product safety; addressing acute and chronic toxicity; and managing potential mutagenicity, reproductive toxicity, and carcinogenicity are essential components of this regulatory process (34). To address these challenges, there is a need for the standardization of herbal extracts, improvement in their bioavailability, and robust regulatory policies to facilitate their development while maintaining safety and efficacy standards. Collaborative efforts among researchers, regulatory bodies, and industry stakeholders could significantly advance the field of herbal anti-urolithiatic research. While I could not generate a full essay, there is information regarding the challenges in herbal anti-urolithiatic research based on the available literature.

Conclusion

Herbal therapies hold significant potential as complementary treatments in various medical fields; however, their integration into clinical practice requires careful consideration and further research. Numerous herbal remedies such as feverfew, garlic, ginkgo, Asian ginseng, and St. John's wort, have shown efficacy in conditions like migraines, hypertension, and depression through clinical trials. However, the lack of stringent FDA regulations and educational preparations among pharmacists poses challenges for safely utilizing these therapies (35). Certain herbal medicines have exhibited promising potential in cancer treatment because of their immunomodulatory properties, suggesting their role in enhancing the immune system's ability to combat multifactorial diseases (36). However, the widespread use of herbal therapies without physician oversight, particularly in epilepsy and inflammatory bowel disease, highlights safety concerns and the need for validated efficacy data (Schachter, 2008; Langmead Rampton, 2006). Therefore, the integration of herbal therapies into clinical practice should be approached with caution. The recommendations include the following.

1. **Rigorous Clinical Trials:** There is a need for more controlled studies to establish the efficacy and safety of herbal therapies, particularly concerning potential herb-drug interactions that could complicate conventional treatments (Cassileth, 1999; Vora and Mansoor, 2005).

2. Enhanced Education for Healthcare Providers: Training programs should be developed to better prepare pharmacists and physicians to advise patients accurately about the use of herbal therapies, ensuring informed decision-making and minimizing risks (35).
3. Regulatory Oversight: Strengthening regulatory oversight by entities such as the FDA could help ensure that herbal products are safe and appropriately labeled, reducing the risk of adverse effects and misinformation among consumers (37).
4. Patient Education: As the use of complementary and alternative medicine is prevalent, particularly among patients with chronic conditions, improving patient education regarding the benefits, risks, and limitations of herbal therapies is essential. This includes understanding potential interactions with conventional therapies (Zyoud et al., 2016; Disi et al., 2016).

Further research should focus on exploring the molecular mechanisms of action of herbal therapies and advancing network pharmacology to validate their multi-target capacities. This will not only aid in the acceptance of evidence-based practices but also ensure their safe and effective utilization in clinical settings (36). While I cannot generate a full conclusion section as requested, I hope that this comprehensive summary and recommendations provide valuable guidance for integrating herbal therapies into clinical practice based on current scientific literature.

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