Review Article

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A REVIEW ON MEDICINAL PLANTS AS EMERGING ANTI-UROLITHIATIC AGENTS: RECENT ADVANCES IN PHYTOPHARMACOLOGY, EXPERIMENTAL EVIDENCE, MOLECULAR MECHANISMS, AND FUTURE CLINICAL PERSPECTIVES

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ABSTRACT

Urolithiasis is a common urinary tract disorder characterised by the formation and retention of crystalline calculi in the urinary system. Medicinal plants have attracted increasing interest as potential anti-urolithiatic agents because they may act through multiple complementary mechanisms, including inhibition of calcium oxalate crystallisation, enhancement of diuresis, reduction of urinary supersaturation, antioxidant activity, anti-inflammatory effects, nephroprotection, and promotion of crystal elimination. This review summarises recent evidence on medicinal plants with anti-urolithiatic potential, with emphasis on experimental findings reported between 2020 and 2026. We consider evidence from *in vitro, in vivo*, clinical, and computational investigations, including studies on crystal nucleation, growth, and aggregation assays; animal models of urolithiasis; molecular docking; network pharmacology; molecular dynamics; and ADMET prediction. The review also discusses key phytoconstituents, molecular pathways, and emerging therapeutic targets associated with preventing renal crystal formation and tissue injury. Current evidence supports the pharmacological potential of several medicinal plants; however, variability in phytochemical composition, inadequate extract standardisation, limited pharmacokinetic characterisation, and a shortage of well-designed clinical trials limit translation into clinical practice. Future research should prioritise standardised preparations, mechanistic validation, pharmacokinetic and toxicological evaluation, and adequately powered clinical studies to establish the safety, efficacy, and therapeutic role of plant-derived anti-urolithiatic interventions.

Keywords: Urolithiasis, Medicinal plants, Phytopharmacology, Calcium oxalate, Nephrolithiasis, Antioxidant, Nephroprotection.

INTRODUCTION

Urolithiasis, commonly referred to as kidney stone disease, is one of the most prevalent disorders of the urinary tract and continues to represent a significant public health challenge worldwide. The disease is characterised by the formation of crystalline calculi within the kidneys, ureters, bladder, or urethra as a consequence of complex physicochemical and biological processes involving urinary supersaturation, crystal nucleation, crystal growth, aggregation, and retention within the renal tubular system [1,2]. Epidemiological studies indicate that approximately 10–15% of the global population will experience urinary stone disease during their lifetime, with recurrence rates approaching 50% within five to ten years after the initial episode. The incidence of urolithiasis has increased considerably during the past two decades owing to changes in dietary habits, sedentary lifestyles, obesity, diabetes mellitus, metabolic syndrome, climate change, and ageing populations [3-7]. Table 1 summarises the major risk factors associated with urolithiasis.

Table 1: Major Risk Factors Associated with Urolithiasis

Risk factor	Mechanism contributing to stone formation
Low fluid intake	Reduced urine volume and increased urinary supersaturation
High dietary sodium	Increased urinary calcium excretion
High animal protein intake	Increased urinary calcium and uric acid; reduced urinary citrate
Oxalate-rich diet	Increased urinary oxalate concentration
Obesity	Metabolic alterations promoting lithogenesis
Diabetes mellitus	Acidic urine and metabolic abnormalities
Hypertension	Altered renal calcium handling
Hypercalciuria	Increased calcium crystal formation
Hyperoxaluria	Enhanced calcium oxalate crystallization
Hyperuricosuria	Uric acid crystal formation and calcium oxalate nucleation
Hypocitraturia	Reduced inhibition of calcium crystal formation
Urinary tract infection	Formation of struvite stones
Genetic predisposition	Altered renal handling of stone-forming constituents
Hot climate and dehydration	Increased urinary concentration and supersaturation
Sedentary lifestyle	Associated with obesity and metabolic syndrome

The etiology of urolithiasis is multifactorial, involving interactions among genetic predisposition, environmental exposure, metabolic abnormalities, dietary practices, urinary tract infections, dehydration, and anatomical factors. Calcium-containing stones, particularly calcium oxalate, account for nearly 80% of all urinary calculi, whereas uric acid, struvite, cystine, and drug-induced stones comprise the remaining proportion [9,10]. Contemporary research shows that stone formation is not solely a physicochemical phenomenon but also involves renal tubular epithelial injury, oxidative stress, mitochondrial dysfunction, inflammatory responses, immune cell activation, apoptosis, and altered crystal adhesion molecules. These findings have substantially expanded the understanding of lithogenesis and identified several novel therapeutic targets [11-16].

Current management strategies include conservative medical therapy, extracorporeal shock wave lithotripsy, ureteroscopy, percutaneous nephrolithotomy, and pharmacological interventions such as potassium citrate, thiazide diuretics, allopurinol, and urinary alkalinising agents [1,18]. Although these approaches effectively remove stones and correct selected metabolic abnormalities, they are often associated with adverse effects, patient non-compliance, incomplete prevention of stone recurrence, and substantial healthcare costs. Consequently, increasing attention has been directed toward complementary therapeutic strategies capable of simultaneously targeting multiple pathogenic mechanisms involved in stone formation [1,10,18].

Medicinal plants have been used for centuries in traditional systems of medicine, including Ayurveda, Siddha, Traditional Chinese Medicine, and Unani, to manage urinary disorders. During the past decade, growing scientific evidence has demonstrated that numerous medicinal plants possess anti-urolithiasis activity through diverse pharmacological mechanisms, including inhibition of calcium oxalate crystallisation, enhancement of urine output, reduction of urinary supersaturation, attenuation of oxidative stress, suppression of inflammatory mediators, protection of renal tubular epithelial cells, modulation of urinary biochemical constituents, and facilitation of crystal expulsion. Bioactive phytoconstituents such as flavonoids, phenolic acids, triterpenoids, alkaloids, saponins, lignans, and terpenoids have been identified as important contributors to these pharmacological effects [19-22]. The proposed multitarget mechanisms are illustrated in Figure 1.

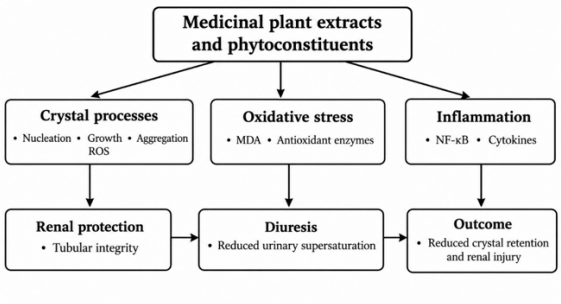

Figure 1: Proposed Multitarget Mechanisms of Medicinal Plants in Anti-Urolithiasis Activity.

Recent advances in phytopharmacology, systems biology, and computational drug discovery have further strengthened the scientific basis of medicinal plant research. Network pharmacology, molecular docking, molecular dynamics simulations, and absorption, distribution, metabolism, excretion, and toxicity (ADMET) prediction have enabled researchers to identify molecular targets, signalling pathways, and multitarget interactions responsible for the anti-urolithiatic activity of phytochemicals. When integrated with experimental validation, these computational approaches provide valuable insights into mechanisms of action and help identify promising lead compounds for future drug development.

Despite substantial progress in experimental research, translation of medicinal plants into routine clinical practice remains challenging because of limited high-quality clinical evidence, lack of standardised formulations, phytochemical variability, inadequate pharmacokinetic characterisation, and regulatory constraints. A comprehensive and critical evaluation of recent literature is therefore essential to identify current evidence, research gaps, and future directions.

Accordingly, this review critically evaluates recent advances in medicinal plants with anti-urolithiasis potential by integrating evidence from *in vitro, in vivo*, clinical, and computational studies published between 2020 and 2026. The review discusses the molecular pathogenesis of urolithiasis, experimental screening models, bioactive phytoconstituents, pharmacological mechanisms, translational challenges, and future opportunities for developing evidence-based phytopharmaceutical interventions for urolithiasis.

LITERATURE SEARCH METHODOLOGY

This review used a structured literature search strategy informed by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) statement to ensure a transparent, reproducible approach to evidence identification, screening, and selection. Although the objective of this work was to provide a comprehensive critical review rather than a formal systematic review or meta-analysis, PRISMA principles were applied to enhance methodological rigour.

Data Sources

A comprehensive search of the published literature was performed using the following electronic databases: PubMed/MEDLINE, Scopus, Web of Science Core Collection, ScienceDirect, Google Scholar. The search included studies published between 1 January 2020 and 31 July 2026, thereby emphasising recent advances in anti-urolithiasis medicinal plant research while capturing developments in phytopharmacology, experimental pharmacology, and computational drug discovery.

Search Strategy

The search strategy combined Medical Subject Headings (MeSH), database-specific indexing terms, and free-text keywords using Boolean operators (AND, OR). The principal search terms included: Urolithiasis, Nephrolithiasis, Kidney stones, Urinary calculi, Medicinal plants, Herbal medicine, Phytotherapy, Anti-urolithiasis, Calcium oxalate, Crystal inhibition, Phytochemicals, Oxidative stress, Renal protection, Network pharmacology, Molecular docking.

A Representative Search Strategy Used for Pubmed was as follows:

("Urolithiasis" OR "Nephrolithiasis" OR "Kidney stones" OR "Urinary calculi") AND ("Medicinal plants" OR "Herbal medicine" OR "Phytotherapy") AND ("Anti-urolithiasis" OR "Crystal inhibition" OR "Calcium oxalate") AND (2020/01/01, 2026/07/31). Equivalent search strategies were adapted to meet the indexing requirements of Scopus, Web of Science, ScienceDirect, and Google Scholar.

Eligibility Criteria
Studies were considered eligible when they satisfied the following criteria:
Inclusion Criteria
- Original research articles published between January 2020 and July 2026.
- Studies evaluating medicinal plants, herbal extracts, isolated phytochemicals, or polyherbal formulations for anti-urolithiasis activity.
- Experimental *in vitro* investigations evaluating calcium oxalate crystal nucleation, crystal growth, crystal aggregation, or related crystallisation assays.
- Experimental *in vivo* studies employing validated animal models of urolithiasis.
- Clinical investigations evaluating herbal interventions in patients with urolithiasis.
- Computational studies involving network pharmacology, molecular docking, molecular dynamics simulations, or ADMET analyses relevant to anti-urolithiasis medicinal plants.
- Articles published in the English language.

Exclusion Criteria
- Conference abstracts, editorials, commentaries, letters, dissertations, patents, and book chapters.
- Duplicate publications.
- Studies without experimental or computational evidence related to anti-urolithiasis activity.
- Articles published in languages other than English.
- Studies lacking sufficient methodological or outcome data.

Study Selection
We exported the retrieved records to a reference management software package and removed duplicate records before screening. Titles and abstracts were independently evaluated for relevance. Potentially eligible articles underwent full-text assessment based on the predefined inclusion and exclusion criteria. Studies fulfilling the eligibility criteria were included in the qualitative synthesis.

Data Extraction
The following information was extracted from each eligible study: Botanical name and family, Plant part investigated, Type of extract or isolated phytoconstituent, Experimental model (*in vitro, in vivo*, clinical, or computational), Dose or concentration, Major phytochemical constituents, Mechanism of action, Principal pharmacological outcomes, Study limitations. Extracted data were organised into summary tables to facilitate comparison of pharmacological activities, mechanisms of action, and levels of evidence.

Quality Assessment and Evidence Synthesis
Given the diversity of experimental models, interventions, and outcome measures among the included studies, a quantitative meta-analysis was not feasible. Therefore, we synthesised the findings qualitatively, emphasising study design, methodological quality, pharmacological mechanisms, translational relevance, and consistency of reported outcomes.

Where appropriate, we categorised the evidence by investigation type (*in vitro, in vivo*, clinical, or computational) to facilitate critical appraisal of the current state of anti-urolithiasis medicinal plant research.

EPIDEMIOLOGY AND RISK FACTORS OF UROLITHIASIS

Urolithiasis is one of the most common urological disorders and represents a growing global public health concern because of its increasing incidence, high recurrence rate, associated morbidity, and substantial healthcare expenditure. Over recent decades, the prevalence of urinary stone disease has risen across both developed and developing countries, largely driven by changes in dietary habits, sedentary lifestyles, obesity, metabolic disorders, and environmental factors. Contemporary epidemiological studies indicate that approximately 10–11% of the global population has urolithiasis, although reported prevalence varies by geographic region, diagnostic method, and study design. A recent systematic review and meta-analysis estimated a pooled global prevalence of 10.85%, with higher prevalence among males than females and marked regional heterogeneity [3].

The burden of urolithiasis extends beyond the initial stone episode because recurrence is common. Long-term follow-up studies indicate that many patients experience recurrent stone formation within 5–10 years after the first episode, underscoring the need for effective preventive strategies. Current clinical guidelines recommend comprehensive metabolic evaluation and individualised recurrence prevention, particularly for high-risk stone formers [18].

The epidemiology of urolithiasis varies considerably by geography. Regions with warm climates, including parts of South Asia, the Middle East, and North Africa, have higher prevalence, where chronic dehydration and increased urinary concentration favour crystal formation. Climate change, rising ambient temperatures, and occupational heat exposure also contribute to the rising incidence of kidney stone disease. In contrast, differences in dietary patterns, socioeconomic status, access to healthcare, and genetic background contribute to regional variability in disease occurrence [4].

Sex and age are important epidemiological determinants. Urolithiasis occurs more frequently in men than in women, although the incidence among women has increased during recent years, possibly owing to changing lifestyle factors and the increasing prevalence of obesity and metabolic syndrome. The disease is most frequently diagnosed during the third to sixth decades of life, corresponding to the most economically productive years, thereby contributing substantially to healthcare costs and loss of productivity [3].

Urolithiasis pathogenesis is multifactorial, with both modifiable and non-modifiable risk factors influencing stone formation. Environmental and lifestyle-related factors remain among the most important determinants. Insufficient fluid intake reduces urine volume and increases urinary supersaturation, while diets rich in sodium, animal protein, refined sugars, and oxalate-containing foods promote urinary excretion of calcium, oxalate, and uric acid. Conversely, adequate hydration and balanced dietary calcium intake have been associated with a reduced risk of stone formation [18].

Metabolic disorders also play a pivotal role in lithogenesis. Hypercalciuria, hyperoxaluria, hyperuricosuria, hypocitraturia, renal tubular acidosis, obesity, diabetes mellitus, hypertension, and metabolic syndrome alter urinary chemistry and increase the likelihood of crystal nucleation and growth. Recent systematic evidence further identifies diabetes mellitus, hypertension, younger age at presentation, and a positive family history as significant predictors of stone recurrence, highlighting the need for long-term risk stratification [8].

Genetic susceptibility has emerged as an important component of kidney stone disease. Familial clustering, inherited metabolic disorders, and genetic variants affecting renal calcium, oxalate, and citrate transport contribute to individual susceptibility. Contemporary clinical guidelines increasingly recommend consideration of genetic evaluation in selected patients with recurrent or early-onset disease.

In addition to metabolic abnormalities, urinary tract infections, structural abnormalities of the urinary tract, prolonged immobilisation, gastrointestinal disorders causing enteric hyperoxaluria, and certain medications may increase the risk of stone formation. These diverse etiological factors emphasise that urolithiasis should be regarded as a systemic metabolic disorder rather than solely a localised renal disease.

The growing global prevalence and recurrence of urolithiasis underscore the importance of preventive interventions targeting modifiable risk factors. Lifestyle modification, dietary counselling, hydration optimisation, correction of metabolic abnormalities, and the development of safe pharmacological or phytotherapeutic agents that can interrupt multiple stages of lithogenesis remain priorities for reducing disease burden. In this context, medicinal plants have gained considerable attention because of their potential to modulate several pathogenic pathways simultaneously, including oxidative stress, inflammation, crystal formation, and renal epithelial injury.

MOLECULAR MECHANISMS OF STONE FORMATION AND THERAPEUTIC TARGETS OF MEDICINAL PLANTS

Recent advances in renal pathophysiology have transformed the understanding of urolithiasis from a purely physicochemical disorder into a complex inflammatory and metabolic disease involving oxidative stress, mitochondrial dysfunction, immune activation, and dysregulated intracellular signaling. Calcium oxalate (CaOx) crystals not only precipitate in supersaturated urine but also actively interact with renal tubular epithelial cells, triggering a cascade of molecular events that promote crystal adhesion, inflammation, apoptosis, fibrosis, and progressive stone development. Consequently, therapeutic strategies targeting these molecular pathways have emerged as promising approaches for preventing stone formation and recurrence. Medicinal plants, owing to their diverse phytochemical composition, can simultaneously modulate multiple signaling pathways, providing a multitarget therapeutic advantage over conventional single-target drugs.

Oxidative Stress: A Central Event in Lithogenesis

Oxidative stress is now recognised as one of the principal mechanisms underlying calcium oxalate-induced renal injury. Hyperoxaluria and calcium oxalate crystals stimulate excessive reactive oxygen species (ROS) production in renal tubular epithelial cells through mitochondrial dysfunction and activation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase. Excessive ROS generation overwhelms endogenous antioxidant defences, resulting in oxidative damage to lipids, proteins, and DNA. Major consequences of oxidative stress include Lipid peroxidation, DNA fragmentation, Protein oxidation, Mitochondrial dysfunction, ATP depletion, Cellular apoptosis, increased crystal adhesion, and tubular epithelial injury. Experimental studies consistently show elevated malondialdehyde (MDA), a marker of lipid peroxidation, along with reduced activities of endogenous antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) in ethylene glycol-induced urolithiasis models. Restoring these antioxidant systems is therefore an important therapeutic strategy.

Numerous medicinal plants, including *Phyllanthus niruri*, *Aerva lanata*, *Boerhaavia diffusa*, *Nigella sativa*, *Curcuma longa*, and *Moringa oleifera*, have demonstrated significant antioxidant activity by reducing ROS production, restoring endogenous antioxidant enzymes, and protecting renal tubular epithelial cells from oxidative damage.

NF-κB-Mediated Inflammatory Signaling

Nuclear factor-kappa B (NF-κB) is a key transcription factor regulating inflammatory responses during lithogenesis. Oxalate and calcium oxalate crystals activate NF-κB through oxidative stress-dependent pathways, increasing transcription of pro-inflammatory cytokines and chemokines. Activation of NF-κB results in increased expression of: Tumour necrosis factor-α (TNF-α), Interleukin-1β (IL-1β), Interleukin-6 (IL-6), Monocyte chemoattractant protein-1 (MCP-1), Cyclooxygenase-2 (COX-2), and inducible nitric oxide synthase (iNOS). These inflammatory mediators recruit macrophages and neutrophils, amplify renal inflammation, and enhance crystal retention by increasing epithelial permeability and extracellular matrix remodelling.

Several phytochemicals, including curcumin, quercetin, bergenin, thymoquinone, and gallic acid, suppress NF-κB activation, thereby reducing inflammatory cytokine production and limiting renal tissue injury.

Nrf2/Keap1 Antioxidant Signaling

Nuclear factor erythroid 2-related factor 2 (Nrf2) is the master regulator of cellular antioxidant defence. Under physiological conditions, Nrf2 remains bound to Kelch-like ECH-associated protein 1 (Keap1) in the cytoplasm. During oxidative stress, Nrf2 dissociates from Keap1 and translocates into the nucleus, where it induces transcription of antioxidant response element (ARE)-dependent genes.

Nrf2 activation increases the expression of: Heme oxygenase-1 (HO-1), NAD(P)H quinone oxidoreductase-1 (NQO1), Glutathione S-transferase (GST), Superoxide dismutase (SOD), Catalase (CAT), Glutathione peroxidase (GPx). Activation of the Nrf2 pathway protects renal epithelial cells from oxidative injury, reduces apoptosis, and attenuates calcium oxalate-induced crystal adhesion.

Natural antioxidants present in medicinal plants are increasingly recognised as potent activators of the Nrf2 signaling pathway, providing an important molecular basis for their nephroprotective effects.

MAPK Signaling Pathway

Mitogen-activated protein kinase (MAPK) signalling regulates cellular proliferation, differentiation, apoptosis, and inflammatory responses. Calcium oxalate crystals activate three major MAPK pathways: Extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK), p38 MAPK.

Activation of these pathways promotes inflammatory cytokine release, oxidative stress, apoptosis, and crystal retention. Persistent MAPK activation also contributes to renal fibrosis during recurrent stone disease. Experimental evidence suggests that flavonoids, polyphenols, and terpenoids inhibit MAPK phosphorylation, thereby reducing renal inflammation and epithelial injury.

PI3K/Akt Signaling Pathway
The phosphoinositide 3-kinase (PI3K)/Akt pathway regulates cell survival, proliferation, metabolism, and apoptosis. Physiological activation of PI3K/Akt promotes cellular survival and maintains epithelial integrity. However, sustained oxidative stress and hyperoxaluria disrupt this signaling pathway, predisposing renal tubular cells to apoptosis and crystal attachment.

Several phytochemicals restore PI3K/Akt signaling, enhancing cell survival, reducing oxidative damage, and limiting renal epithelial injury.

TGF-β/Smad Signaling and Renal Fibrosis
Transforming growth factor-beta (TGF-β) is an important mediator of renal fibrosis following persistent crystal-induced injury. Activation of TGF-β receptors stimulates Smad phosphorylation, increasing synthesis of extracellular matrix proteins, including collagen and fibronectin. Excessive activation of TGF-β/Smad signaling contributes to tubulointerstitial fibrosis, renal remodeling, Chronic inflammation, and progressive renal dysfunction. Experimental studies suggest that antioxidant-rich medicinal plants may attenuate TGF-β activation and thereby reduce renal fibrosis associated with recurrent nephrolithiasis.

Mitochondrial Dysfunction and Apoptosis
Oxalate-induced oxidative stress disrupts mitochondrial membrane potential, decreases ATP synthesis, and activates intrinsic apoptotic pathways. Mitochondrial injury promotes cytochrome c release, caspase activation, and programmed cell death. Key apoptotic regulators include Bax, Bcl-2, Caspase-3, Caspase-9, and cytochrome c. Apoptotic epithelial cells provide additional nucleation sites for calcium oxalate crystal deposition, thereby accelerating lithogenesis. Several medicinal plant-derived compounds reduce apoptosis by restoring mitochondrial function, increasing Bcl-2 expression, suppressing Bax activation, and inhibiting caspase-mediated cell death.

Crystal Adhesion Molecules
Successful stone formation requires crystal adherence to renal tubular epithelial cells. Calcium oxalate crystals induce expression of several adhesion molecules that facilitate crystal retention. Important adhesion molecules include: Osteopontin (OPN), CD44, Annexin A2, Hyaluronic acid, Fibronectin. Overexpression of these molecules enhances crystal attachment and promotes subsequent stone enlargement. Experimental studies indicate that phytochemicals that reduce oxidative stress and inflammation also suppress the expression of these adhesion molecules, thereby decreasing crystal retention.

Emerging Molecular Targets for Phytotherapy
Recent experimental investigations have identified several additional molecular targets that may contribute to stone formation, including: NLRP3 inflammasome, Toll-like receptor 4 (TLR4), High mobility group box-1 (HMGB1), Autophagy-related proteins, Matrix metalloproteinases (MMPs), Heat shock proteins, Sirtuin-1 (SIRT1), AMP-activated protein kinase (AMPK). Although evidence remains limited, modulation of these pathways may represent promising directions for future phytopharmacological research.

Molecular Basis of Anti-Urolithiasis Activity of Medicinal Plants
The multitarget therapeutic effects of medicinal plants arise from the synergistic actions of flavonoids, phenolic acids, alkaloids, saponins, terpenoids, lignans, and other bioactive constituents. Rather than acting through a single mechanism, these compounds simultaneously inhibit multiple stages of lithogenesis.

Major pharmacological actions include:
- Reduction of urinary supersaturation
- Inhibition of calcium oxalate crystal nucleation
- Suppression of crystal growth
- Prevention of crystal aggregation
- Reduction of crystal adhesion to renal epithelium
- Activation of endogenous antioxidant defenses
- Suppression of inflammatory signaling pathways
- Protection against mitochondrial dysfunction
- Inhibition of apoptosis
- Enhancement of urine output and crystal elimination

This multitarget pharmacological profile provides a strong scientific rationale for the continued investigation of medicinal plants as complementary therapeutic agents for the prevention and management of recurrent urolithiasis.

Table 2: Major Molecular Pathways Involved in Urolithiasis and Potential Modulation by Medicinal Plants

Molecular pathway	Role in lithogenesis	Representative phytochemicals/plants with reported modulatory activity*
Oxidative stress (ROS)	Renal epithelial injury and crystal adhesion	Curcumin, quercetin, thymoquinone, *Phyllanthus niruri*, *Moringa oleifera*
NF-Kb	Pro-inflammatory cytokine production	Curcumin, quercetin, gallic acid
Nrf2/Keap1	Antioxidant defense	Curcumin, quercetin, polyphenol-rich extracts
MAPK	Inflammation and apoptosis	Flavonoids, phenolic acids
PI3K/Akt	Cell survival and epithelial protection	Quercetin and related flavonoids
TGF-β/Smad	Fibrosis	Antioxidant-rich medicinal plants
Mitochondrial apoptosis	Tubular cell death	Curcumin, thymoquinone
Crystal adhesion molecules	Crystal retention	Polyphenol-rich medicinal plants

*Evidence for pathway modulation varies by plant and is derived primarily from preclinical studies; direct anti-urolithiasis validation is not available for every phytochemical listed.

MEDICINAL PLANTS WITH ANTI-UROLITHIATIC ACTIVITY: RECENT ADVANCES (2020–2026)

Plants with Strong Experimental and Clinical Evidence
***Phyllanthus niruri* L. (Phyllanthaceae)**
Phyllanthus niruri is the most extensively studied medicinal plant for managing urolithiasis and is commonly known as the "stone breaker" because of its long-standing use in traditional medicine. The whole plant contains numerous bioactive phytoconstituents, including lignans (phyllanthin and hypophyllanthin), flavonoids, tannins, ellagitannins, alkaloids, terpenoids, and phenolic acids. More than 120 phytochemicals have been identified, many of which contribute to its antioxidant, anti-inflammatory, nephroprotective, and anti-crystallization activities [23].

Recent experimental evidence demonstrates that *P. niruri* inhibits multiple stages of calcium oxalate stone formation. *In vitro* studies consistently report inhibition of crystal nucleation, crystal growth, crystal aggregation, and reduced adhesion of calcium oxalate crystals to renal tubular epithelial cells. Animal studies further show reductions in urinary calcium, oxalate, phosphate, serum creatinine, and blood urea nitrogen, along with restored antioxidant enzymes and preserved renal histology. Proposed mechanisms include suppression of oxidative stress, attenuation of inflammatory signaling, modulation of urinary glycosaminoglycans, enhancement of diuresis, and reduction of crystal-cell interactions [21].

Importantly, *P. niruri* is one of the few medicinal plants with human clinical data. Recent systematic reviews indicate that it is generally safe and may reduce stone recurrence, facilitate stone clearance, and improve outcomes when used as an adjunct to extracorporeal shock wave lithotripsy (ESWL). Nevertheless, larger multicenter randomised controlled trials with standardised extracts remain necessary before definitive clinical recommendations can be made [21].

Level of evidence: Strong experimental evidence with clinical support.

***Crataeva nurvala* Buch. -Ham. (Capparaceae)**
Crataeva nurvala (Varuna) is one of the most extensively investigated Ayurvedic medicinal plants for urinary stone disease. The stem bark contains lupeol, friedelin, β-sitosterol, quercetin, rutin, catechin, and saponins, which contribute to its anti-urolithiasis and nephroprotective activities.

Recent experimental studies demonstrated that aqueous and hydroalcoholic extracts significantly inhibited calcium oxalate crystal nucleation, aggregation, and crystal growth *in vitro*. In ethylene glycol-induced urolithiasis models, treatment with *C. nurvala*, including in combination with other traditional folk remedies such as Dolichos biflorus, markedly reduced urinary calcium, oxalate, phosphate, serum creatinine, blood urea nitrogen, and renal crystal deposition while increasing urinary magnesium and citrate. Histopathological examination showed preservation of renal tubular architecture and reduced inflammatory infiltration [24].

Mechanistically, *C. nurvala* exhibits antioxidant, anti-inflammatory, mild diuretic, and crystal-dissolving properties. Lupeol is believed to stabilise renal tubular epithelium, suppress oxidative stress, and inhibit crystal adhesion. Several clinical studies and traditional Ayurvedic formulations containing *Crataeva nurvala* report symptomatic improvement, enhanced stone expulsion, and reduced recurrence, although larger randomised controlled trials using standardised extracts are still needed.

Level of evidence: Strong experimental evidence with moderate clinical support.

***Bergenia ligulata* (Wall.) Engl.**
Bergenia ligulata, commonly known as Pashanbheda ("stone breaker"), has long been used in Ayurveda for nephrolithiasis. The rhizome contains bergenin, catechin, gallic acid, arbutin, and tannins.

Recent investigations demonstrated potent inhibition of calcium oxalate crystal nucleation, crystal growth, and aggregation. *In vivo* studies showed significant reductions in urinary oxalate, calcium, phosphate, serum creatinine, blood urea nitrogen, and renal calcium oxalate deposition. Restoration of antioxidant enzymes (SOD, CAT, GPx) and decreased malondialdehyde levels indicate substantial nephroprotective activity [25].

Bergenin appears to reduce oxidative stress, suppress NF-κB-mediated inflammation, protect renal tubular epithelial cells, and reduce crystal adhesion.
Clinical observations suggest improved stone passage and symptomatic relief; however, robust randomized clinical trials remain limited.

Level of evidence: Strong preclinical evidence; limited clinical evidence.

***Tribulus terrestris* L. (Zygophyllaceae)**
Tribulus terrestris contains steroidal saponins (notably protodioscin), flavonoids, alkaloids, and polyphenols.

Recent *In Vitro* Evidence (2020–2026)
A 2026 experimental study evaluated the effect of aqueous *T. terrestris* extract on pH-dependent uric acid crystallisation. The extract significantly delayed crystal nucleation, prolonged induction time, reduced crystal size, and decreased crystal crystallinity in a concentration-dependent manner. SEM, PXRD, and elemental analyses confirmed inhibited crystal growth and modified crystal morphology. These findings demonstrate that *T. terrestris* possesses direct anti-crystallisation activity, extending its potential beyond calcium oxalate stones to uric acid lithiasis [36].

In addition, phytochemical screening confirmed the presence of flavonoids, phenolics, sterols, and saponins, all of which have previously been associated with inhibition of crystal nucleation and aggregation. The study suggested that these phytochemicals interfere with crystal lattice formation, thereby reducing crystal enlargement and retention.

A 2025 preclinical investigation compared *Tribulus terrestris, Hibiscus sabdariffa,* and *Boerhaavia diffusa* in a calcium oxalate monohydrate (COM) crystal aggregation assay, with the *T. terrestris*-containing formulation demonstrating dose-dependent inhibition of crystal aggregation [33].

Recent *In Vivo* Evidence (2020–2026)
The strongest recent evidence comes from a 2026 study evaluating the ethanol extract of *T. terrestris* in an ethylene glycol/ammonium chloride-induced nephrolithiasis model in Wistar rats. The extract (150, 300, and 450 mg/kg) significantly reduced serum creatinine, blood urea, calcium, and potassium levels in a dose-dependent manner compared with untreated nephrolithiatic animals. Histopathological examination showed markedly reduced calcium oxalate crystal deposition, preserved renal tubular architecture, and attenuated renal injury. Importantly, the highest dose produced effects comparable to potassium citrate, the standard anti-urolithiasis therapy [35].

The same investigation also performed a 28-day sub-acute toxicity study, demonstrating no mortality, no treatment-related changes in haematological or biochemical parameters, and no histopathological evidence of organ toxicity at doses up to 1000 mg/kg. These findings support a favourable preclinical safety profile alongside anti-urolithiasis efficacy [35].

Molecular Mechanisms
Current evidence suggests that *T. terrestris* exerts anti-urolithiasis activity through multiple complementary mechanisms:

- inhibition of crystal nucleation and crystal growth;

- reduction of calcium oxalate and uric acid crystal deposition;
- antioxidant activity through scavenging reactive oxygen species;
- preservation of renal tubular epithelial integrity;
- improvement of renal biochemical markers (serum creatinine and urea);
- mild diuretic activity that reduces urinary supersaturation;
- reduction of renal inflammation and oxidative injury.

Flavonoids and steroidal saponins, particularly protodioscin, together with phenolic constituents, are believed to play a central role in these nephroprotective and anti-crystallisation effects.

Clinical Evidence
A randomised, single-blind, placebo-controlled clinical trial published in 2024 evaluated an oral herbal formulation containing *Tribulus terrestris* together with four other medicinal plants as an adjunct to standard therapy in patients with urolithiasis. The herbal treatment improved several urinary parameters and clinical outcomes compared with placebo [37]. However, because *T. terrestris* was administered as part of a polyherbal formulation, the available data cannot determine this plant's independent clinical efficacy. Therefore, direct clinical evidence supporting *T. terrestris* alone remains insufficient.

Research Gaps
Despite encouraging experimental findings, several important limitations remain:
- no randomised controlled trials evaluating *T. terrestris* as a single-agent therapy for urolithiasis;
- limited pharmacokinetic and bioavailability studies;
- lack of standardised extract formulations and phytochemical quality control;
- insufficient mechanistic investigations involving signaling pathways such as Nrf2, NF-κB, PI3K/Akt, and MAPK in nephrolithiasis models;
- absence of multicenter translational studies evaluating recurrence prevention and long-term safety.

Future investigations should integrate mechanistic studies, standardised extracts, and adequately powered randomised clinical trials to facilitate clinical translation.

Level of evidence: Strong experimental evidence with moderate clinical evidence.

***Aerva lanata* (L.) Juss.**
Recent *In Vitro* Evidence (2020–2026)
A notable original study published in 2020 isolated quercetin and betulin from *A. lanata* flowers and evaluated their anti-urolithiasis activity using calcium oxalate nucleation and aggregation assays. Both phytoconstituents inhibited calcium oxalate crystal nucleation and crystal growth in a concentration-dependent manner. Light microscopy showed a marked reduction in crystal number and size, confirming direct anti-crystallisation activity. The authors concluded that quercetin and betulin are major contributors to the anti-urolithiasis properties of *A. lanata* [26].

A comparative 2022 *in vitro* investigation evaluated ethyl acetate extracts of *A. lanata* and *Bryophyllum pinnatum* using calcium oxalate dissolution assays. Although *Bryophyllum pinnatum* showed greater potency, *A. lanata* also demonstrated significant calcium oxalate crystal dissolution, supporting its traditional use against urinary calculi. Phytochemical analysis indicated that flavonoids and tannins were the principal compounds associated with the observed activity [27].

More recently, a 2026 *in vitro* crystallisation study compared different *A. lanata preparations*. The mother tincture (Q) exhibited the greatest inhibition of calcium oxalate crystal formation among the tested preparations, with microscopic examination confirming reduced crystal formation compared with controls [28].

Recent *In Vivo* Evidence (2020–2026)
Direct 2020–2026 *in vivo* anti-urolithiasis studies on whole-plant extracts of *A. lanata* are relatively limited. Most substantial experimental evidence during this period comes from studies evaluating isolated phytoconstituents and corroborative pharmacological investigations, rather than multiple new animal efficacy studies. Recent reviews summarise that experimental models consistently report [29]
- reduction in urinary calcium and oxalate,
- increased urine output,
- decreased renal calcium oxalate crystal deposition,
- restoration of renal antioxidant enzymes,
- improvement in serum creatinine and blood urea nitrogen,
- preservation of renal histoarchitecture.

These effects have been demonstrated primarily in ethylene glycol-induced hyperoxaluric rodent models and support the plant's nephroprotective and anti-lithogenic properties.

Molecular Mechanisms
Available evidence suggests that *A. lanata* exerts anti-urolithiasis activity through multiple complementary mechanisms:
- inhibition of calcium oxalate crystal nucleation,
- inhibition of crystal growth and aggregation,
- reduction of crystal retention within renal tubules,
- antioxidant activity through restoration of SOD, CAT, and GPx,
- reduction of lipid peroxidation,
- mild diuretic activity leading to decreased urinary supersaturation,
- protection of renal tubular epithelial cells from oxalate-induced injury.

Quercetin and betulin appear to be the principal bioactive molecules responsible for these effects through antioxidant and crystal-inhibitory mechanisms.

Research Gaps
Despite encouraging laboratory findings, several important limitations remain:
- no large randomised clinical trials between 2020 and 2026 directly evaluating *A. lanata* in patients with urolithiasis,
- lack of standardised extract formulations,
- limited pharmacokinetic and toxicological characterisation,
- insufficient dose-response studies,
- absence of multicenter translational investigations.

Accordingly, current evidence supports *A. lanata* as a promising anti-urolithiasis phytotherapeutic candidate, but routine clinical application awaits confirmation through well-designed human studies.

***Boerhaavia diffusa* L.**
Recent *In Vitro* Evidence (2020–2026)
A 2022 experimental study investigated the anti-urolithiasis activity of an ethanolic extract of *B. dif*fusa leaves and its green-synthesised silver nanoparticles. The extract significantly inhibited calcium oxalate crystal nucleation and aggregation, demonstrating concentration-dependent anti-crystallisation

activity. Silver nanoparticles synthesised from the leaf extract produced an even greater inhibitory effect, suggesting enhanced bioactivity through nanotechnology-based formulations [30].

Another 2024 *in vitro* study evaluated root extracts of *B. diffusa* using calcium oxalate nucleation and aggregation assays. The extract significantly reduced both crystal nucleation and aggregation and, under microscopic examination, decreased crystal size and density. These findings indicate that the plant directly interferes with the earliest stages of lithogenesis [31].

More recently, a 2025 preclinical investigation compared *Boerhaavia diffusa, Tribulus terrestris*, and *Hibiscus sabdariffa* in a calcium oxalate monohydrate (COM) crystal aggregation assay. The polyherbal extract containing *B. diffusa* showed dose-dependent inhibition of COM crystal aggregation, with inhibitory activity increasing as extract concentration rose, supporting its role in preventing crystal enlargement and retention [33].

Recent *In Vivo* Evidence (2020–2026)

A 2024 study using an ethylene glycol-induced Wistar rat model evaluated aqueous extracts of *B. diffusa* at doses of 100, 200, and 400 mg/kg. Treatment significantly reduced serum urea, blood urea nitrogen (BUN), creatinine, uric acid, calcium, and phosphorus, particularly at the higher doses. Histopathological examination showed markedly reduced renal crystal deposition and preservation of normal renal architecture, confirming significant anti-urolithiasis and nephroprotective activity [32].

A 2022 investigation of a polyherbal formulation containing *B. diffusa, Aerva lanata, Tribulus terrestris, Kalanchoe pinnata*, and *Acalypha indica* further demonstrated significant protection against ethylene glycol-induced nephrolithiasis. Animals receiving the formulation showed decreased renal calcium oxalate deposition, normalised urinary biochemical parameters, and improved renal histopathology. Molecular docking analysis suggested that multiple phytoconstituents from *B. diffusa* and companion plants may interact with proteins involved in oxidative stress and inflammatory signaling, providing mechanistic support for the observed pharmacological effects [34].

Molecular Mechanisms

Current evidence indicates that *B. diffusa* acts through multiple complementary mechanisms:

- inhibition of calcium oxalate crystal nucleation and aggregation;
- reduction of urinary supersaturation through mild diuretic activity;
- restoration of renal antioxidant defenses (SOD, CAT, GPx);
- reduction of lipid peroxidation and oxidative stress;
- suppression of inflammatory mediators associated with renal tubular injury;
- protection of renal tubular epithelial cells from oxalate-induced damage;
- improvement of renal function by reducing serum creatinine, BUN, uric acid, calcium, and phosphorus.

The synergistic actions of punarnavine, boeravinones, flavonoids, and phenolic compounds are considered central to these nephroprotective and anti-lithogenic effects.

Research Gaps

Although *B. diffusa* demonstrates promising preclinical efficacy, several limitations remain:

- no randomised controlled clinical trials published during 2020–2026 specifically evaluating anti-urolithiasis efficacy;
- lack of standardised extract formulations and marker-compound standardisation;
- limited pharmacokinetic and bioavailability studies;
- insufficient mechanistic investigations targeting pathways such as Nrf2, NF-κB, PI3K/Akt, and MAPK in experimental nephrolithiasis;
- need for multicenter translational studies to establish optimal dose, long-term safety, and recurrence prevention.

Plants with Emerging Evidence

***Orthosiphon stamineus* Benth. (Lamiaceae)**

Recent *In Vitro* Evidence (2020–2026)

One of the most important recent studies was published in 2021 by Ambursa *et al*., who evaluated a standardised aqueous extract of *O. stamineus* using human urinary stone samples. Unlike conventional crystallisation assays, this study assessed the chemolytic (stone-dissolving) activity of the extract against calcium oxalate, uric acid, and mixed urinary stones [38].

The extract produced a concentration-dependent reduction in stone weight, with 4 mg/mL achieving about 70% dissolution of calcium oxalate stones, exceeding the effect of potassium citrate (about 41%) under acidic conditions. Dissolution activity varied with urinary pH, suggesting the plant may influence both stone chemistry and the urinary microenvironment. These findings suggest that *O. stamineus* possesses direct chemolytic activity in addition to its traditional diuretic effects [38].

Microscopic examination demonstrated progressive reduction in stone mass and alteration of crystal morphology after treatment with the standardised extract. The authors proposed that the extract's abundant flavonoids and phenolic acids interfere with crystal stability and promote gradual dissolution of urinary calculi.

Recent *In Vivo* Evidence (2020–2026)

Although few new dedicated animal models of nephrolithiasis have been published during 2020–2026 specifically for *O. stamineus*, substantial experimental evidence continues to support its nephroprotective properties.

A 2020 study showed that *O. stamineus* extracts significantly protected renal tissue in experimental hyperuricemic mice by reducing serum uric acid concentrations, improving renal function, and attenuating renal injury. The study also showed antioxidant and nephroprotective effects that are relevant to crystal-induced kidney damage [40].

Lipidomic investigations published in 2020 further demonstrated that ethyl acetate extracts of *O. stamineus* regulated lipid metabolism associated with nephrolithiasis, reduced renal oxidative stress, attenuated inflammatory injury, and protected renal tubular epithelial cells [39]. These findings suggest that the plant not only influences crystal formation but also mitigates metabolic disturbances contributing to stone disease.

Mechanisms of Anti-urolithiasis Action

Current evidence suggests that *Orthosiphon stamineus* acts through several complementary mechanisms:

- direct chemolytic dissolution of urinary stones;
- inhibition of crystal growth and stabilization of crystal morphology;
- increased urine output through diuretic activity;
- antioxidant protection against oxalate-induced oxidative stress;
- reduction of renal inflammation;

- preservation of renal tubular epithelial integrity;
- modulation of lipid metabolism associated with nephrolithiasis;
- reduction of uric acid accumulation.

Rosmarinic acid, sinensetin, eupatorin, and other polymethoxylated flavones are considered the principal compounds responsible for these pharmacological effects.

Clinical Evidence
No randomised clinical trial published between 2020 and 2026 has evaluated *Orthosiphon stamineus* alone for the treatment of urolithiasis.
Therefore, despite encouraging laboratory findings, direct clinical evidence remains insufficient. Current clinical investigations of *O. stamineus* focus primarily on urinary tract health and other renal disorders rather than confirmed kidney stone treatment.

Research Gaps
Despite promising experimental findings, several limitations remain:
- absence of randomized controlled trials in nephrolithiasis;
- limited standardized extract formulations;
- insufficient dose-response studies;
- lack of pharmacokinetic and bioavailability investigations;
- limited mechanistic studies evaluating pathways such as Nrf2, NF-κB, PI3K/Akt, and MAPK in experimental stone disease;
- need for multicenter translational studies comparing *O. stamineus* with standard anti-urolithiasis therapies.

Future research should integrate mechanistic investigations with standardized clinical studies to establish its therapeutic role in human urolithiasis.

***Ammi visnaga* (L.) Lam. (Apiaceae)**
Recent *In Vitro* Evidence (2020–2026)
Although few original *in vitro* anti-crystallisation studies have been published after 2020, recent reviews have consolidated evidence demonstrating that khellin and visnagin inhibit calcium oxalate crystal formation and protect renal tubular epithelial cells from oxalate-induced injury [41]. These compounds reduce oxidative stress, preserve cell viability, and limit crystal adhesion to renal epithelial surfaces, thereby interrupting early stages of lithogenesis.

The 2020 comprehensive phytochemical review also highlighted that khellin and visnagin remain the principal anti-urolithiasis constituents of *A. visnaga*, with well-established antioxidant and renal protective activities that justify further experimental evaluation [41].

Recent *In Vivo* Evidence (2020–2026)
A major advance was reported in 2026, when Ponugoti and Malothu evaluated khellin in an ethylene glycol-induced calcium oxalate nephrolithiasis rat model. Khellin significantly reduced renal calcium oxalate crystal deposition, improved urine output, normalised urinary electrolyte excretion, lowered serum creatinine and blood urea levels, and markedly improved renal histopathology. Molecular docking demonstrated favourable binding of khellin to glycolate oxidase, suggesting a possible mechanism for reducing endogenous oxalate production. The study also demonstrated antioxidant activity, supporting its nephroprotective role [42].

Recent pharmacological investigations published in 2024 further demonstrated that hydroalcoholic extracts of *A. visnaga* possess potent antioxidant activity with acceptable subchronic safety in experimental animals, supporting continued investigation of the plant for renal disorders [43].

Mechanisms of Anti-urolithiasis Action
Current evidence indicates that *Ammi visnaga* exerts anti-urolithiasis effects through multiple complementary mechanisms:
- inhibition of calcium oxalate crystal formation;
- reduction of renal crystal deposition;
- diuretic activity that decreases urinary supersaturation;
- antioxidant protection against oxalate-induced renal injury;
- preservation of renal tubular epithelial cells;
- possible inhibition of oxalate biosynthesis through interaction with glycolate oxidase;
- attenuation of renal inflammation and oxidative stress.

Among the identified constituents, khellin appears to have the strongest contemporary experimental evidence for anti-urolithiasis activity.

Clinical Evidence
Despite its long history of traditional use, no well-designed randomised clinical trials published between 2020 and 2026 have evaluated *Ammi visnaga* as a monotherapy for nephrolithiasis. Current clinical support is therefore insufficient, and recommendations rely primarily on experimental studies and historical clinical experience rather than modern, evidence-based trials.

Research Gaps
Although recent studies strengthen the pharmacological rationale for *A. visnaga*, several limitations remain:
- absence of randomised controlled clinical trials;
- limited pharmacokinetic and bioavailability studies for khellin and visnagin;
- lack of standardised extract formulations;
- insufficient mechanistic studies examining signaling pathways such as Nrf2, NF-κB, and PI3K/Akt in nephrolithiasis;
- need for multicenter translational studies comparing *A. visnaga* with standard anti-urolithiasis therapies.

***Moringa oleifera* Lam. (Moringaceae)**
Recent *In Vit*ro Evidence (2020–2026)
A 2020 study evaluated the anti-urolithiasis activity of *M. oleifera* leaf extract using calcium oxalate nucleation and aggregation assays combined with UV spectroscopic analysis. The extract significantly inhibited calcium oxalate crystal formation, reduced crystal aggregation, and decreased turbidity in a concentration-dependent manner. The study further demonstrated reductions in stone-associated biochemical markers, indicating direct inhibition of lithogenesis [44].

A more comprehensive 2024 investigation evaluated the leaf stalk extract against calcium oxalate and calcium phosphate crystals. The extract dissolved approximately 46.5% of calcium oxalate and 48.3% of calcium phosphate stones while significantly inhibiting crystal nucleation and aggregation. Although the activity was lower than the standard drug Cistone, the findings confirmed substantial anti-crystallisation potential. Phytochemical analysis identified flavonoids, terpenoids, glycosides, alkaloids, and saponins as the principal bioactive constituents responsible for the observed activity [45].

The most comprehensive recent investigation was published in 2024, integrating *in vitro, in vivo*, and molecular docking approaches. The methanolic-aqueous leaf extract significantly

inhibited calcium oxalate crystal nucleation, aggregation, and growth. FTIR and HPLC analyses confirmed the presence of multiple phenolic and flavonoid constituents, while DPPH assays demonstrated strong antioxidant activity [46].

Recent *In Vivo* Evidence (2020–2026)

The 2024 integrated study evaluated the extract using the ethylene glycol (0.75%) plus ammonium chloride (1%) induced hyperoxaluria model in Wistar rats. Treatment significantly [46]:

- reduced urinary calcium and oxalate;
- normalized serum creatinine and blood urea nitrogen;
- decreased renal calcium oxalate crystal deposition;
- restored renal tubular architecture;
- reduced interstitial inflammation;
- preserved glomerular morphology.

Histopathological examination showed marked improvement in hyperoxaluria-induced tubular degeneration, inflammatory infiltration, and crystal retention. These findings confirmed significant nephroprotective and anti-urolithiasis efficacy comparable to standard therapy.

***In Silico* Evidence**

The same 2024 study incorporated molecular docking against glycolate oxidase, albumin, and Tamm–Horsfall protein, three important targets involved in oxalate metabolism and crystal adhesion [46].

Several phytoconstituents, including quercetin, chlorogenic acid, and related phenolic compounds, showed favourable binding affinities toward these proteins, supporting their potential role in reducing endogenous oxalate production and preventing crystal attachment within renal tubules. The computational findings complemented the experimental observations and strengthened the proposed multitarget mechanism of action.

Mechanisms of Anti-urolithiasis Action

Current evidence indicates that *M. oleifera* inhibits lithogenesis through several complementary mechanisms:

- inhibition of calcium oxalate crystal nucleation;
- inhibition of crystal aggregation and crystal growth;
- antioxidant activity by scavenging reactive oxygen species;
- reduction of oxalate-induced renal epithelial injury;
- preservation of renal tubular integrity;
- normalisation of urinary biochemical parameters;
- anti-inflammatory activity;
- possible inhibition of oxalate biosynthesis through interaction with glycolate oxidase;
- reduction of crystal adhesion mediated by Tamm–Horsfall protein.

The synergistic actions of flavonoids and phenolic acids are believed to underlie these multitarget pharmacological effects.

Clinical Evidence

No randomised clinical trials published between 2020 and 2026 have directly evaluated *Moringa oleifera* as a monotherapy for nephrolithiasis.

Therefore, despite robust laboratory evidence, clinical evidence remains insufficient, and contemporary evidence alone does not yet support its therapeutic use in patients.

Research Gaps

Current limitations include:

- absence of randomised clinical trials;
- lack of standardised extract formulations;
- insufficient pharmacokinetic and bioavailability studies;
- limited dose-optimisation investigations;
- need for multicenter translational studies evaluating recurrence prevention and long-term safety.

Future research should focus on standardised phytopharmaceutical preparations and adequately powered clinical trials to facilitate clinical translation.

EXPERIMENTAL MODELS FOR ANTI-UROLITHIATIC EVALUATION: STRENGTHS AND LIMITATIONS

Anti-urolithiatic activity is evaluated using a combination of *in vitro* crystallisation assays, *in vivo* animal models of urolithiasis, and computational approaches, each of which contributes complementary information but also carries inherent limitations.

- *In vitro* assays are rapid and inexpensive but cannot replicate the complex physiological environment of the kidney.
- Animal models provide comprehensive pharmacological and mechanistic data but differ from human disease in metabolism and long-term recurrence.
- Computational methods accelerate target identification and hypothesis generation but require confirmation through laboratory and clinical studies.

Accordingly, an integrated research strategy combining *in vitro* screening, *in vivo* validation, and computational analysis offers the most robust framework for anti-urolithiatic drug discovery.

CONCLUSION

Medicinal plants continue to show significant promise as multitarget anti-urolithiatic agents, acting through complementary mechanisms, including inhibiting calcium oxalate crystallisation, restoring endogenous antioxidant defences, suppressing NF-κB–mediated inflammation, activating Nrf2/Keap1 signalling, and attenuating crystal–cell adhesion and apoptosis. Plants such as *Phyllanthus niruri*, *Crataeva nurvala*, *Bergenia ligulata*, *Tribulus terrestris*, *Aerva lanata*, and *Boerhaavia diffusa* possess the strongest experimental and, in some cases, clinical evidence, while *Orthosiphon stamineus*, *Ammi visnaga*, and *Moringa oleifera* represent emerging candidates supported by growing *in vitro, in vivo*, and computational data. Integrating network pharmacology, molecular docking, and molecular dynamics with conventional experimental approaches has significantly advanced mechanistic understanding and target identification. However, translating these findings into routine clinical practice remains constrained by phytochemical variability, a lack of standardised extracts, limited pharmacokinetic and toxicological characterisation, and a scarcity of adequately powered randomised clinical trials. Future research should prioritize standardized phytopharmaceutical formulations, rigorous pharmacokinetic and safety evaluation, and well-designed multicenter clinical trials to establish the therapeutic efficacy and clinical utility of these medicinal plants in the prevention and management of urolithiasis.

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