

Pharmacological Investigation of Traditional Medicinal Plants for the Management of Urolithiasis

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ABSTRACT

Urolithiasis remains a prevalent and recurrent urinary disorder characterized by the formation of crystalline deposits within the renal system. Despite advancements in surgical and pharmacological interventions, current therapeutic options often fail to prevent recurrence and may be associated with undesirable adverse effects. Consequently, traditional medicinal plants have gained increasing attention as safe, multitargeted alternatives for long-term management of kidney stone disease. This review provides a comprehensive evaluation of the pharmacological potential of key traditional medicinal plants including *Tribulus terrestris*, *Crataeva nurvala*, *Bergenia ligulata*, *Phyllanthus niruri*, *Boerhaavia diffusa*, and *Didymocarpus pedicellate* which have been historically used in Ayurveda, Unani, Traditional Chinese Medicine, and ethnomedicine for the treatment of urinary calculi. The phytochemical constituents of these plants, such as flavonoids, phenolics, lignans, saponins, terpenoids, alkaloids, and triterpenoids, exhibit litholytic, diuretic, antioxidant, anti-inflammatory, and crystal-modifying activities. Experimental evidence demonstrates their ability to inhibit calcium oxalate nucleation, growth, and aggregation; reduce urinary supersaturation; protect renal epithelial cells from oxalate-induced oxidative injury; and modulate inflammatory responses. In vivo hyperoxaluria models further validate their nephroprotective effects and ability to normalize urinary biochemical parameters. Emerging clinical studies suggest promising benefits in reducing stone size, recurrence, and associated symptoms, although further standardized, large-scale trials are required. Overall, the review highlights the mechanistic basis, therapeutic relevance, and future potential of medicinal plants as effective, safe, and affordable phytotherapeutic agents for the prevention and management of urolithiasis.

Keywords: Urolithiasis, Medicinal plants, Phytochemicals, Calcium oxalate crystallization, Nephroprotection

INTRODUCTION

Urolithiasis, commonly referred to as kidney stone disease, is a chronic and recurrent disorder characterized by the formation of crystalline concretions within the urinary tract. It represents a significant global health burden, affecting approximately 10-15% of the population worldwide, with marked geographic, climatic, and dietary influences on its prevalence [1,2]. The incidence of urolithiasis has shown a steady rise over the past few decades, particularly in developing as well as industrialized nations, largely due to changes in lifestyle, dietary habits, obesity, and metabolic disorders [3]. Epidemiological evidence indicates a higher prevalence in males compared to females, with

peak occurrence between the third and fifth decades of life; however, a growing trend among pediatric and elderly populations has also been reported [4]. The high recurrence rate, reaching nearly 50% within 5-10 years after the first episode, further contributes to the clinical and economic burden imposed by this disease [5]. The pathophysiology of kidney stone formation is a complex, multifactorial process involving supersaturation of urine with stone-forming constituents, nucleation, crystal growth, aggregation, and retention within the renal tubules [6]. Calcium oxalate stones represent nearly 70-80% of all urinary calculi, followed by calcium phosphate, uric acid, struvite, and cystine stones [7]. Multiple endogenous and exogenous factors influence stone formation, including hypercalciuria, hyperoxaluria,

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hypocitraturia, urinary pH alterations, oxidative stress, and urinary tract infections [8]. Renal epithelial injury induced by reactive oxygen species further facilitates crystal adhesion and retention, thereby accelerating stone development [9]. Thus, urolithiasis is now increasingly recognized not merely as a physicochemical disorder but also as a condition involving cellular, oxidative, and inflammatory mechanisms. Despite advances in medical and surgical management, the current therapeutic strategies for urolithiasis remain limited in their ability to prevent recurrence effectively. Conventional treatments include extracorporeal shock wave lithotripsy, ureteroscopy, percutaneous nephrolithotomy, and pharmacological agents such as thiazide diuretics, potassium citrate, and allopurinol [10,11]. While these approaches are effective in stone removal and metabolic correction, they do not entirely eliminate the risk of recurrence and are often associated with adverse effects including electrolyte imbalance, gastrointestinal disturbances, renal injury, and patient non-compliance [12]. Moreover, surgical interventions are costly, may require repeated procedures, and carry risks of infection, hemorrhage, and renal tissue damage [13]. These limitations highlight the urgent need for safer, cost-effective, and long-term preventive strategies for the management of urolithiasis. In this context, there has been a growing resurgence of interest in plant-based pharmacological interventions derived from traditional medicinal systems such as Ayurveda, Unani, Traditional Chinese Medicine, and ethnomedicine [14]. Numerous medicinal plants have been historically used for the treatment and prevention of urinary stones due to their diuretic, litholytic, antioxidant, anti-inflammatory, and crystallization-inhibitory properties [15]. Phytoconstituents such as flavonoids, saponins, alkaloids, terpenoids, and phenolic compounds have demonstrated significant antiurolithiatic activity in experimental and clinical studies [16]. Unlike synthetic drugs, plant-based remedies are generally considered to exhibit fewer side effects and provide a multitargeted therapeutic approach by modulating oxidative stress, urinary supersaturation, and renal epithelial integrity [17]. This has led to intensified pharmacological investigations aimed at validating the traditional claims and identifying bioactive compounds responsible for antiurolithiatic effects.

The purpose of the present review is to critically evaluate the pharmacological evidence supporting the use of traditional medicinal plants in the management of urolithiasis. The review aims to integrate available experimental and clinical data to elucidate the mechanisms of action, efficacy, and safety of selected medicinal plants with antiurolithiatic potential. By bridging traditional knowledge with modern scientific validation, this review seeks to provide a comprehensive understanding of plant-based therapeutics as promising alternatives or adjuncts to conventional therapies. The significance of this work lies in its potential to facilitate the development of novel phytopharmaceutical agents that are effective, affordable, and safer for long-term management and prevention of urolithiasis.

2. Pathophysiology Of Urolithiasis

Urolithiasis is a heterogeneous disorder characterized by the formation of crystalline concretions within the urinary tract, differing widely in chemical composition, morphology, and etiopathogenesis. Calcium-containing stones are the most prevalent type, accounting for nearly 75–80% of all renal calculi. Among these, calcium oxalate stones are the most dominant and exist in two crystalline forms, calcium oxalate monohydrate and calcium oxalate dihydrate, which differ in their physicochemical stability and biological behavior [18]. Calcium phosphate stones, primarily composed of hydroxyapatite and brushite, are strongly associated with alkaline urinary pH and renal tubular acidosis [19]. Uric acid stones constitute approximately 5–10% of kidney stones and develop mainly due to persistent acidic urine, hyperuricosuria, dehydration, and metabolic syndrome. These stones are radiolucent and show a strong correlation with insulin resistance and gout [20]. Struvite stones, made up of magnesium ammonium phosphate, are infection-related calculi that form in alkaline urine due to the activity of urease-producing microorganisms such as *Proteus* and *Klebsiella* species [21]. Cystine stones are rare and occur due to cystinuria, a hereditary defect in renal tubular reabsorption of cystine, leading to recurrent and difficult-to-treat stone formation [22]. The diversity in stone composition indicates that urolithiasis is a multifactorial metabolic disorder influenced by biochemical, infectious, and genetic determinants.

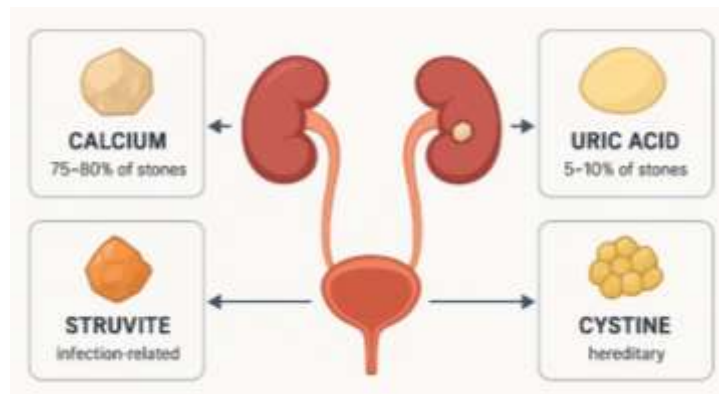


Figure 1. Pathophysiology of urolithiasis showing major types of urinary calculi: calcium (75–80%), uric acid (5–10%), struvite (infection-related), and cystine (hereditary), highlighting their key metabolic and pathological determinants.

Mechanisms of Stone Formation

The pathogenesis of kidney stone formation is a multistep physicochemical and cellular process involving urinary supersaturation, nucleation, crystal growth, aggregation, and renal retention. Urinary supersaturation is the fundamental thermodynamic driving force for crystallization and occurs when the concentration of stone-forming constituents such as calcium, oxalate, phosphate, and uric acid exceeds their solubility product [23]. Supersaturation is influenced by urinary volume, pH, dietary intake, ionic composition, and the balance between crystallization promoters and inhibitors. Dehydration and low urine output significantly elevate supersaturation and therefore markedly increase the risk of stone formation [24]. Nucleation represents the initial formation of solid crystal nuclei from supersaturated urine. This process may occur through homogeneous nucleation under conditions of extreme supersaturation or, more commonly, through heterogeneous nucleation on renal epithelial surfaces, cellular debris, or urinary macromolecules such as Tamm–Horsfall protein and osteopontin [25]. Once nuclei are formed, crystal growth ensues through the continuous deposition of ions onto the crystal surface. Crystal growth is governed by urinary ionic activity, pH, temperature, and the presence of natural inhibitors such as citrate and magnesium that regulate crystal size and stability [26]. Aggregation follows crystal growth and involves the adhesion of individual microcrystals into larger conglomerates. This process markedly increases the probability of stone retention by enlarging particle size and reducing the likelihood of spontaneous urinary elimination [27]. Aggregation

is facilitated by damaged epithelial surfaces, reduced urinary inhibitors, and interaction with matrix proteins. Retention of crystals within the renal tubules is a critical step in stone pathogenesis. Under physiological conditions, small crystals are eliminated through urine flow; however, oxidative and inflammatory injury to renal epithelial cells enhances crystal adherence and internalization [28]. The development of Randall’s plaques, which are subepithelial deposits of calcium phosphate at the renal papillae, provides anchoring platforms for calcium oxalate overgrowth, leading to macroscopic stone formation [29]. Crystal-induced tubular obstruction further increases intratubular pressure, perpetuating local supersaturation and creating a self-sustaining cycle of stone growth and recurrence [30].

Role of Oxidative Stress, Inflammation, and Genetic Factors

Oxidative stress plays a pivotal role in the initiation and progression of urolithiasis. Exposure of renal epithelial cells to oxalate and calcium oxalate crystals induces excessive generation of reactive oxygen species, which leads to lipid peroxidation, mitochondrial dysfunction, DNA damage, and apoptosis [31]. Oxidative injury disrupts cellular integrity and exposes underlying extracellular matrix components that act as binding sites for crystal attachment and retention [32]. Experimental studies have shown that oxalate-mediated oxidative stress significantly enhances crystal-cell interactions and promotes intrarenal crystal deposition. Inflammation is closely integrated with oxidative mechanisms in stone disease. Calcium oxalate crystals activate

inflammatory pathways, including nuclear factor-kappa B, mitogen-activated protein kinases, and NLRP3 inflammasome complexes, resulting in increased production of cytokines such as tumor necrosis factor- α , interleukin-1 β , and interleukin-6 [33]. These mediators enhance leukocyte infiltration, epithelial damage, and fibrosis, thereby facilitating crystal aggregation and retention [34]. Chronic low-grade inflammation is now recognized as a major contributor to recurrent stone formation and progressive renal tissue remodeling. Genetic predisposition also plays an important role in individual susceptibility to urolithiasis. Several monogenic disorders such as cystinuria, primary hyperoxaluria, and Dent's disease directly lead to recurrent and severe stone disease [35]. In addition, polymorphisms in genes regulating calcium transport, oxalate metabolism, urinary citrate excretion, and inflammatory responses have been linked to increased stone risk [36]. Genome-wide association studies have identified multiple genetic loci associated with calcium oxalate and uric acid stones, highlighting the polygenic nature of common urolithiasis [37].

Targets for Pharmacological Intervention

The multifactorial pathophysiology of urolithiasis provides numerous molecular and physiological targets for pharmacological intervention. Reduction of urinary supersaturation remains a principal therapeutic goal and is achieved by increasing urine volume, reducing the excretion of stone-forming solutes, and correcting metabolic abnormalities [38]. Inhibition of nucleation, crystal growth, and aggregation constitutes a key preventive strategy. Agents that enhance urinary citrate and magnesium levels effectively suppress calcium oxalate crystallization and facilitate stone dissolution [39]. Oxidative stress and inflammation have emerged as critical therapeutic targets. Antioxidants that neutralize reactive oxygen species preserve renal epithelial integrity and significantly reduce crystal adhesion and tubular injury [40]. Anti-inflammatory agents that suppress cytokine production and inflammasome activation further limit crystal-induced epithelial damage and stone recurrence [41]. Additionally, molecular modulation of crystal-binding proteins such as osteopontin, annexin II, and hyaluronic acid receptors has been proposed as a novel strategy for preventing crystal retention within

the renal tubules [42]. Traditional medicinal plants exert pharmacological effects on multiple pathogenic pathways simultaneously. Many plant-derived phytoconstituents possess diuretic, antioxidant, anti-inflammatory, and crystallization-inhibitory activities, enabling a multitargeted therapeutic action that is superior to single-target synthetic drugs [43]. These properties form the pharmacological basis for the increasing scientific investigation of medicinal plants in the management of urolithiasis.

3. Traditional Medicinal Plants in The Management Of Urolithiasis

Overview of Ethnobotanical Use

The use of medicinal plants for the prevention and treatment of urolithiasis has been documented for several millennia across diverse traditional systems of medicine. Long before the advent of modern pharmacotherapy, plant-based remedies constituted the primary therapeutic approach for urinary calculi in ancient medical traditions such as Ayurveda, Traditional Chinese Medicine, Unani, and various African and indigenous folk medical systems. These traditional practices were based on empirical observations accumulated over generations and are increasingly being validated through modern pharmacological and experimental investigations [44]. In Ayurveda, urolithiasis is described under the condition known as *Ashmari*, which is considered one of the most difficult urinary disorders to manage. Classical Ayurvedic texts such as the *Charaka Samhita* and *Sushruta Samhita* provide detailed descriptions of the etiology, clinical manifestations, and plant-based treatments for urinary stones. Numerous medicinal plants such as *Crataeva nurvala*, *Tribulus terrestris*, *Bergenia ligulata*, and *Boerhaavia diffusa* have been traditionally prescribed for dissolving stones, promoting urine output, and alleviating pain and inflammation associated with urolithiasis [45]. These plants are classified under various therapeutic groups including diuretics (*Mutravirechaniya*), stone-breaking agents (*Ashmari bhedana*), and urinary tract tonics, highlighting the holistic approach of Ayurvedic therapeutics. Traditional Chinese Medicine (TCM) also recognizes urolithiasis as a disorder of fluid metabolism, heat accumulation, and stagnation within the urinary tract. In TCM theory, kidney stones are associated with

damp-heat syndromes and impaired qi flow in the bladder meridian. Herbal formulations containing plants such as *Desmodium styracifolium*, *Plantago asiatica*, *Pyrrosia lingua*, and *Lysimachia christinae* have been extensively used to promote diuresis, clear heat, remove dampness, and facilitate stone expulsion [46]. Modern experimental studies have confirmed that several of these herbs exhibit significant diuretic, antioxidant, and crystallization-inhibitory effects, thereby supporting their traditional use. The Unani system of medicine, which originated from Greco-Arab traditions, also provides a comprehensive description of urolithiasis under the condition known as *Hisat-e-Kulya* or *Hisat-e-Masana*. Unani physicians have historically employed medicinal plants such as *Tribulus terrestris*, *Dolichos biflorus*, *Raphanus sativus*, and *Withania somnifera* for their litholytic, diuretic, and nephroprotective properties [47]. These remedies were administered either as single-drug preparations or as polyherbal formulations aimed at correcting humoral imbalances, dissolving calculi, and preventing recurrence. In African traditional medicine and various indigenous folk systems across Asia, South America, and the Middle East, a wide range of locally available plants have been used to manage urinary stone disease. Ethnobotanical surveys conducted in different geographical regions have documented the use of plants such as *Phyllanthus niruri*, *Aerva lanata*, *Herniaria hirsuta*, *Paronychia argentea*, and *Cymbopogon citratus* for the treatment of urolithiasis [48,49]. These plants are often consumed as aqueous decoctions or infusions and are believed to act by increasing urine flow, reducing crystal aggregation, and alleviating inflammation and pain. The widespread geographical distribution of ethnomedicinal practices for urolithiasis underscores the universal recognition of plant-based therapies as an effective and accessible treatment option. A striking feature of traditional antiurolithiatic therapy is the repeated appearance of certain plant families across different cultures and medical systems. Families such as Asteraceae, Fabaceae, Poaceae, Lamiaceae, Euphorbiaceae, and Apiaceae are among the most frequently reported sources of medicinal plants for stone disease [50]. Plants belonging to these families are particularly rich in bioactive phytochemicals such as flavonoids, saponins, alkaloids, terpenoids, tannins, and phenolic acids,

many of which exhibit diuretic, antioxidant, anti-inflammatory, and crystallization-modulating properties [51]. The convergence of traditional knowledge and phytochemical composition strongly suggests a pharmacological basis for their therapeutic efficacy. The continued reliance on traditional medicinal plants for the management of urolithiasis, especially in rural and resource-limited settings, reflects not only cultural inheritance but also the limitations of conventional therapies regarding cost, accessibility, and recurrence prevention. Ethnobotanical knowledge thus serves as a valuable foundation for the scientific exploration of novel antiurolithiatic agents. Systematic documentation and pharmacological validation of these traditional claims have become essential for identifying safe, effective, and affordable plant-derived therapeutics for long-term management of urolithiasis [52].

Criteria for Selecting Plants for Pharmacological Studies

The scientific investigation of traditional medicinal plants for antiurolithiatic activity requires a rational and systematic selection strategy to ensure pharmacological relevance, reproducibility, and translational value. One of the most fundamental criteria for plant selection is ethnomedicinal relevance. Plants that have been repeatedly documented across different traditional medical systems and geographical regions for the treatment of urinary stones are considered strong candidates for pharmacological evaluation. Ethnomedicinal usage provides a historical foundation that reflects long-term empirical safety and therapeutic efficacy. Traditional prescriptions recorded in Ayurveda, Traditional Chinese Medicine, Unani medicine, and African folk medicine often serve as primary leads for selecting investigational plants [52]. The frequency of citation in ethnobotanical surveys, the consistency of therapeutic claims, and the specificity of use for urinary stone disorders are critical parameters used to prioritize medicinal plants for experimental studies [53,54]. Plants such as *Phyllanthus niruri*, *Bergenia ligulata*, *Crataeva nurvala*, and *Tribulus terrestris* are classical examples that have progressed from ethnomedicinal use to extensive pharmacological validation due to their strong historical association with urolithiasis [55].

Another major criterion for plant selection is the availability of preliminary *in vitro* and *in vivo* experimental evidence supporting antiurolithiatic potential. *In vitro* crystallization models evaluating nucleation, crystal growth, and aggregation of calcium oxalate serve as rapid and cost-effective screening tools for identifying plants with crystallization-inhibitory activity [56]. *In vivo* animal models, particularly ethylene glycol-induced hyperoxaluria in rats, provide critical insights into the ability of plant extracts to reduce stone burden, normalize urinary biochemical parameters, and protect renal tissue from crystal-induced injury [57]. Plants demonstrating consistent activity across both *in vitro* and *in vivo* models are prioritized for advanced pharmacological and mechanistic investigations. The reproducibility of results, dose-dependency of responses, and comparison with standard antiurolithiatic drugs such as potassium citrate and thiazide diuretics further strengthen the scientific rationale for plant selection [58]. The presence of bioactive chemical constituents with known pharmacological properties represents an equally critical criterion in plant selection. Phytochemical profiling plays a central role in identifying plants enriched with secondary metabolites capable of modulating key pathways involved in stone pathogenesis. Flavonoids, saponins, alkaloids, terpenoids, tannins, and phenolic compounds have been extensively reported to exhibit diuretic, antioxidant, anti-inflammatory, and crystallization-modifying activities [59]. Plants rich in flavonoids are particularly attractive for antiurolithiatic studies because these compounds effectively scavenge reactive oxygen species, protect renal epithelial cells, and inhibit calcium oxalate crystal aggregation [60]. Saponins possess surface-active properties that can reduce crystal adherence and promote disintegration of stone aggregates, whereas alkaloids and terpenoids contribute to smooth muscle relaxation and facilitation of stone expulsion [61]. In addition to qualitative phytochemical composition, quantitative abundance of active constituents and extract standardization are essential considerations for plant selection. Plants exhibiting high concentrations of pharmacologically relevant metabolites and good extraction yield offer practical advantages for reproducible experimental investigations and future drug development. Advanced analytical techniques

such as high-performance liquid chromatography, liquid chromatography–mass spectrometry, and nuclear magnetic resonance spectroscopy are increasingly employed to characterize bioactive fractions and guide bioassay-directed isolation of lead compounds [62]. Standardization based on marker compounds ensures batch-to-batch consistency and enhances the credibility of pharmacological findings. Safety and toxicological profile also represent indispensable criteria in selecting plants for pharmacological investigation. Although ethnomedical use provides preliminary assurance of safety, systematic toxicological studies are necessary to establish safe dose ranges and identify potential organ-specific toxicities. Acute and sub-chronic toxicity studies following international guidelines provide essential information for dose selection in experimental models and future clinical translation [63]. Plants demonstrating a high margin of safety alongside significant pharmacological activity are considered ideal candidates for further development as phytotherapeutic agents. Furthermore, ecological availability and sustainability influence plant selection for long-term pharmacological research. Plants that are endangered, slow-growing, or ecologically vulnerable present challenges for large-scale experimental and clinical investigations. Preference is therefore given to species that are widely distributed, easily cultivable, and renewable without threatening biodiversity [64]. This ensures ethical utilization of plant resources and supports sustainable drug discovery initiatives. Collectively, the integration of ethnomedical relevance, preliminary experimental evidence, phytochemical richness, safety profile, and ecological sustainability provides a comprehensive framework for the rational selection of medicinal plants for antiurolithiatic pharmacological studies. Such a systematic approach enhances the likelihood of identifying efficacious and safe plant-derived therapeutic agents for the long-term management of urolithiasis.

4. Phytochemicals and Their Mechanisms In Anti-Urolithiatic Activity

The therapeutic efficacy of traditional medicinal plants in the management of urolithiasis is primarily attributed to the diverse array of bioactive phytochemicals present within them. These secondary metabolites exert multifaceted pharmacological

actions by modulating urinary biochemistry, suppressing oxidative and inflammatory injury, and directly interfering with the physicochemical processes of stone formation. Among the most extensively investigated phytochemical classes with anti-urolithiatic potential are phenolics and flavonoids, saponins, alkaloids, triterpenoids, polysaccharides, and essential oils. These compounds act synergistically to inhibit crystallization, promote crystal dissolution, enhance diuresis, and protect renal tissue.

Phenolics and Flavonoids

Phenolic compounds and flavonoids represent one of the most important classes of phytochemicals implicated in anti-urolithiatic activity. These compounds are abundantly present in plants such as *Phyllanthus niruri*, *Bergenia ligulata*, *Crataeva nurvala*, and *Tribulus terrestris*. Their primary mechanism of action is attributed to their potent antioxidant activity, which enables them to scavenge reactive oxygen species generated during oxalate-induced renal epithelial injury [65]. By reducing oxidative stress, phenolics and flavonoids preserve the integrity of tubular epithelial cells and prevent exposure of cellular binding sites that facilitate crystal adhesion. In addition to antioxidant effects, flavonoids modulate calcium oxalate crystallization by chelating free calcium ions and reducing urinary supersaturation. Experimental studies have demonstrated that flavonoid-rich extracts significantly inhibit calcium oxalate nucleation, crystal growth, and aggregation in vitro [66]. These compounds also regulate the expression of crystal-binding proteins such as osteopontin and Tamm-Horsfall protein, thereby reducing crystal retention in renal tubules [67]. Furthermore, flavonoids exhibit mild diuretic activity, which contributes to increased urine output and mechanical flushing of microcrystals from the urinary tract [68].

Saponins

Saponins are surface-active glycosides widely distributed in medicinal plants traditionally used for urolithiasis, including *Crataeva nurvala*, *Asparagus racemosus*, and *Herniaria hirsuta*. The anti-urolithiatic activity of saponins is primarily attributed to their ability to reduce surface tension between

crystals, thereby inhibiting crystal aggregation and promoting disintegration of preformed calculi [69]. By disrupting crystal-crystal and crystal-cell interactions, saponins significantly decrease the size and number of stone aggregates. Saponins also enhance diuresis by increasing glomerular filtration rate and promoting electrolyte excretion, thereby reducing urinary supersaturation of stone-forming ions [70]. In vivo studies using ethylene glycol-induced hyperoxaluria models have shown that saponin-rich extracts significantly reduce urinary oxalate levels, renal crystal deposition, and histopathological damage [71]. Additionally, saponins exhibit moderate anti-inflammatory activity, which further contributes to protection against crystal-induced tubular injury.

Alkaloids

Alkaloids constitute a diverse group of nitrogen-containing secondary metabolites with significant pharmacological relevance in urolithiasis. Plants such as *Berberis vulgaris*, *Phyllanthus amarus*, and *Rauwolfia serpentina* contain alkaloids that exhibit nephroprotective and anti-crystallization properties. The anti-urolithiatic activity of alkaloids is mediated through multiple mechanisms, including modulation of urinary pH, inhibition of oxalate synthesis, and smooth muscle relaxation of the urinary tract [72]. Alkaloids also exert antioxidant effects by suppressing lipid peroxidation and improving endogenous antioxidant enzyme activity, thereby reducing renal epithelial injury [73]. Some alkaloids have been reported to interfere with calcium transport channels and calcium-binding proteins, leading to reduced availability of free calcium for stone formation [74]. Their spasmolytic action on ureteral smooth muscle also facilitates the expulsion of small calculi and prevents urinary obstruction.

Triterpenoids

Triterpenoids are widely distributed in medicinal plants such as *Centella asiatica*, *Crataeva nurvala*, *Terminalia arjuna*, and *Boswellia serrata*. These compounds exhibit pronounced anti-inflammatory, antioxidant, and membrane-stabilizing properties that contribute significantly to their anti-urolithiatic effects [75]. Triterpenoids suppress the activation of nuclear factor-kappa B and cyclooxygenase-2

pathways, leading to reduced production of pro-inflammatory cytokines and prostaglandins involved in crystal-induced renal inflammation [76]. Triterpenoids also enhance antioxidant defense by upregulating superoxide dismutase, catalase, and glutathione peroxidase activities in renal tissue. By limiting oxidative and inflammatory damage, they prevent epithelial injury and subsequent crystal adherence [77]. Some triterpenoids have also been shown to inhibit calcium oxalate crystal growth and improve urinary citrate levels, further inhibiting stone formation.

Polysaccharides

Plant-derived polysaccharides represent another important class of bioactive compounds with emerging anti-urolithiatic potential. Polysaccharides isolated from plants such as *Plantago major*, *Bergenia ligulata*, and *Astragalus membranaceus* have demonstrated significant inhibitory effects on calcium oxalate crystallization [78]. These macromolecules interact with growing crystal surfaces, altering crystal morphology and reducing crystal size and aggregation. Polysaccharides also exhibit strong antioxidant and immunomodulatory properties. They reduce oxalate-induced oxidative stress, suppress inflammatory mediator release, and enhance renal tubular cell viability [79]. Furthermore, their high molecular weight and hydrophilic nature facilitate crystal dispersion and urinary elimination, thereby reducing crystal retention within renal tubules.

Essential Oils

Essential oils are volatile mixtures of terpenes, alcohols, aldehydes, and phenolic compounds present in aromatic medicinal plants such as *Cymbopogon citratus*, *Nigella sativa*, *Ocimum sanctum*, and *Foeniculum vulgare*. These oils exhibit significant diuretic, antioxidant, antimicrobial, and antispasmodic activities that contribute to their anti-urolithiatic effects [80]. The diuretic action of essential oils increases urine output and reduces the concentration of lithogenic substances, thereby lowering urinary supersaturation. Infection-induced stones, particularly struvite calculi, are effectively targeted by the antimicrobial activity of essential oils, which inhibit urease-producing bacteria and prevent

alkalinization of urine [81]. Additionally, essential oils suppress inflammatory mediators and reduce oxidative damage to renal tissue, further limiting conditions that favor stone formation and retention.

Proposed Mechanisms of Anti-urolithiatic Action

The collective anti-urolithiatic mechanisms of plant-derived phytochemicals involve a coordinated modulation of multiple pathogenic pathways. Antioxidant activity plays a central role by neutralizing reactive oxygen species and preventing oxalate-induced renal epithelial injury, which is essential for crystal adhesion and retention. Diuretic effects enhance urine flow and decrease urinary supersaturation of calcium, oxalate, and uric acid, thereby reducing nucleation frequency. Direct crystal-modulating actions, including inhibition of nucleation, suppression of crystal growth, prevention of aggregation, and promotion of crystal dissolution, are mediated by several phytochemicals through chelation of calcium ions and alteration of crystal surface properties. Anti-inflammatory mechanisms further limit renal tissue injury and leukocyte infiltration, reducing sites for crystal anchoring and subsequent stone development [82]. The multitargeted pharmacological actions of phytochemicals provide a strong scientific rationale for the use of traditional medicinal plants as effective and safe therapeutic agents for long-term management of urolithiasis.

5. Pharmacological Evaluation of Key Traditional Medicinal Plants

(Divide into sub-sections; include both experimental evidence and mechanisms)

Tribulus terrestris

Tribulus terrestris L. (Zygophyllaceae), commonly known as Gokshura, puncture vine, or caltrop, is one of the most widely used medicinal plants in traditional systems of medicine for the management of urolithiasis. It is extensively described in Ayurveda, Unani, and Traditional Chinese Medicine for its diuretic, litholytic, and nephroprotective properties. The fruits, roots, and aerial parts of the plant are traditionally employed either alone or as components of polyherbal formulations for treating urinary calculi

and other urinary tract disorders. The pharmacological activity of *T. terrestris* is attributed to a diverse spectrum of bioactive phytoconstituents. The plant is particularly rich in steroidal saponins, with protodioscin, dioscin, tribulosin, and terrestrosin being the major active principles. In addition to saponins, the plant contains significant amounts of flavonoids such as quercetin and kaempferol, alkaloids including harmaline and norharmaline, glycosides, tannins, and essential fatty acids [83]. These constituents collectively contribute to the multifaceted antiurolithiatic activity of the plant. Extensive in vitro investigations have demonstrated that extracts of *T. terrestris* significantly inhibit calcium oxalate crystallization. Studies evaluating nucleation, crystal growth, and aggregation have shown that aqueous and alcoholic extracts of the plant reduce the formation of calcium oxalate monohydrate crystals and interfere with crystal aggregation in a concentration-dependent manner. The inhibition of crystal growth is believed to occur through chelation of free calcium ions by saponins and flavonoids, leading to a reduction in urinary supersaturation. Furthermore, the extracts have been shown to modify crystal morphology, resulting in the formation of smaller, less adhesive crystals that are more easily excreted in urine. The in vivo antiurolithiatic activity of *T. terrestris* has been validated using multiple experimental animal models. In the ethylene glycol-induced hyperoxaluria model in rats, oral administration of *T. terrestris* extract significantly reduced urinary oxalate, calcium, and phosphate levels while restoring urinary magnesium and citrate concentrations [89]. Histopathological examination of renal tissue from treated animals revealed a marked reduction in crystal deposition, tubular dilatation, and interstitial inflammation compared to untreated hyperoxaluric controls. These findings confirm the protective effect of *T. terrestris* against oxalate-induced renal injury and stone formation. The diuretic activity of *T. terrestris* is one of its most important pharmacological properties contributing to its antiurolithiatic efficacy. Experimental studies have shown that administration of the plant extract markedly increases urine output and promotes electrolyte excretion without causing significant electrolyte imbalance [84]. The increased urine flow rate reduces urinary supersaturation of lithogenic substances and facilitates the mechanical flushing of

microcrystals from the urinary tract, thereby preventing their retention and subsequent growth into macroscopic stones. Antioxidant activity constitutes another critical mechanism by which *T. terrestris* exerts renoprotective and antiurolithiatic effects. Oxalate-induced stone formation is strongly associated with excessive generation of reactive oxygen species, which damage renal epithelial cells and promote crystal adhesion. Extracts of *T. terrestris* have been shown to significantly decrease lipid peroxidation and enhance the activity of endogenous antioxidant enzymes such as superoxide dismutase, catalase, and glutathione peroxidase in renal tissues [85]. By suppressing oxidative stress, the plant preserves epithelial integrity and reduces sites for crystal retention. In addition to its antioxidant action, *T. terrestris* exhibits notable anti-inflammatory activity. Studies have demonstrated that treatment with the plant extract significantly reduces the expression of pro-inflammatory cytokines such as tumor necrosis factor- α and interleukin-1 β in hyperoxaluric animals. This anti-inflammatory effect limits leukocyte infiltration, tubular injury, and fibrosis, thereby attenuating the pathological microenvironment that favors recurrent stone formation. The combined diuretic, antioxidant, and crystallization-inhibitory actions of *T. terrestris* provide a strong pharmacological basis for its traditional use in urolithiasis. The multitargeted nature of its activity distinguishes it from conventional single-target synthetic drugs and supports its potential as a safe and effective phytotherapeutic agent for long-term management and prevention of kidney stones. However, despite substantial experimental evidence, well-designed clinical trials remain limited, and further investigations are required to establish standardized dosing regimens and confirm long-term safety in human subjects [86].

Crataevanurvala

Crataeva nurvala Buch-Ham. (family Capparaceae), commonly known as Varuna, is a well-documented medicinal plant in Ayurveda and Unani systems for the treatment of urinary tract disorders, particularly urolithiasis. The bark, leaves, and roots of the plant are traditionally used as litholytic, diuretic, and anti-inflammatory agents. Classical Ayurvedic texts describe *C. nurvala* as a specific remedy for the

dissolution of urinary calculi and for restoring normal urinary function, and its use is deeply integrated into several traditional polyherbal formulations for kidney stone management. The pharmacological activity of *C. nurvala* is attributed to the presence of bioactive constituents such as triterpenoids including lupeol and betulinic acid, saponins, flavonoids, tannins, glucosinolates, and sterols. Lupeol, in particular, has been identified as a principal active compound responsible for the antiurolithiatic and anti-inflammatory effects of the plant. These phytoconstituents act synergistically to modulate urinary biochemistry, suppress inflammation, and inhibit stone formation. Experimental studies have consistently demonstrated the potent antiurolithiatic activity of *C. nurvala*. In ethylene glycol- and ammonium chloride-induced hyperoxaluria models in rats, administration of aqueous and alcoholic bark extracts significantly reduced urinary calcium, oxalate, and phosphate concentrations while restoring magnesium levels. These biochemical changes were accompanied by a marked reduction in renal calcium oxalate crystal deposition. Histopathological evaluation of renal tissue showed significant protection against tubular damage, interstitial inflammation, and crystal-induced epithelial injury in treated animals. The plant also exhibits a strong inhibitory effect on calcium oxalate crystallization processes. In vitro crystallization assays have revealed that *C. nurvala* bark extract significantly suppresses nucleation, crystal growth, and aggregation of calcium oxalate in a dose-dependent manner [87]. The saponins and triterpenoids present in the plant are believed to interact with crystal surfaces, thereby altering crystal morphology and preventing the formation of large, adherent aggregates. This direct crystal-modulating action represents a key mechanism underlying its litholytic activity. Anti-inflammatory activity is another critical pharmacological property of *C. nurvala* that contributes to its therapeutic efficacy in urolithiasis. Oxalate-induced renal injury is characterized by intense inflammatory responses, which promote further crystal adherence and fibrosis. Experimental studies have demonstrated that *C. nurvala* significantly suppresses inflammatory mediators such as prostaglandins, tumor necrosis factor- α , and interleukin-6 in renal tissues. Lupeol isolated from the bark has been shown to inhibit cyclooxygenase and

lipooxygenase pathways, thereby reducing renal inflammation and protecting against progressive tubular injury. In addition to its anti-inflammatory effects, *C. nurvala* exhibits pronounced antioxidant activity. Oxidative stress plays a pivotal role in renal epithelial damage during stone formation. Treatment with *C. nurvala* extract has been shown to significantly reduce lipid peroxidation while enhancing the activities of endogenous antioxidant enzymes such as superoxide dismutase, catalase, and glutathione peroxidase in hyperoxaluric animals [87]. This antioxidant defense preserves epithelial integrity and limits the formation of crystal attachment sites. Clinical evidence also supports the antiurolithiatic efficacy of *C. nurvala*. In controlled clinical investigations involving patients with recurrent calcium oxalate stones, administration of standardized *C. nurvala* bark preparations resulted in a significant reduction in stone size and recurrence rate, along with improvement in urinary symptoms such as dysuria and hematuria. The plant was found to be well tolerated, with no significant adverse effects reported during prolonged administration, highlighting its suitability for long-term phytotherapeutic use. Collectively, the antiurolithiatic efficacy of *Crataeva nurvala* is mediated through multiple complementary mechanisms, including inhibition of crystal nucleation and aggregation, modulation of urinary biochemical parameters, diuretic activity, suppression of oxidative stress, and attenuation of inflammation. The convergence of strong experimental and emerging clinical evidence establishes *C. nurvala* as one of the most promising traditional medicinal plants for the pharmacological management of urolithiasis [88].

Bergenia ligulata (Pashanbheda)

Bergenia ligulata (Wall.) Engl. (family Saxifragaceae), commonly known as Pashanbheda, meaning “stone breaker,” is one of the most important lithotriptic medicinal plants described in the classical Ayurvedic system of medicine. The rhizome of the plant is extensively used in traditional formulations for the treatment of urolithiasis, dysuria, urinary tract infections, and renal inflammation. Its ethnomedicinal use is widely documented among indigenous communities in the Himalayan regions of India, Nepal, and Tibet, where decoctions and powders of the rhizome are traditionally administered for

dissolving kidney and bladder stones [100]. The long-standing traditional use of *B. ligulata* as a litholytic agent has provided a strong basis for its modern pharmacological investigation. Phytochemical studies of *B. ligulata* rhizome have revealed the presence of several bioactive constituents, including bergenin, arbutin, catechin, gallic acid, tannins, flavonoids, and triterpenoids. Among these, bergenin is considered the principal active compound responsible for the antiurolithiatic and antioxidant activities of the plant [89]. These phytoconstituents act synergistically to modulate urinary chemistry, suppress oxidative stress, and inhibit the physicochemical processes involved in stone formation. The lithotriptic activity of *B. ligulata* has been extensively validated through in vitro and in vivo experimental models. In vitro crystallization studies have demonstrated that aqueous and alcoholic extracts of the rhizome significantly inhibit calcium oxalate nucleation, crystal growth, and aggregation in a concentration-dependent manner. The extract has been shown to alter crystal morphology, resulting in the formation of smaller and less adherent calcium oxalate crystals, thereby reducing their tendency to aggregate and adhere to renal tubular epithelium. This direct interference with crystal dynamics provides experimental support for its traditional designation as a stone-dissolving agent [90]. In vivo studies using ethylene glycol-induced hyperoxaluric rat models have further confirmed the potent antiurolithiatic activity of *B. ligulata*. Administration of the rhizome extract resulted in a significant reduction in urinary oxalate, calcium, and phosphate levels, along with a marked increase in urinary magnesium concentration. These biochemical changes were associated with a substantial decrease in renal crystal deposition and restoration of normal renal histoarchitecture. Histopathological examination of renal tissue from treated animals revealed reduced tubular dilatation, epithelial degeneration, and interstitial inflammation when compared with untreated hyperoxaluric controls. Oxidative stress is a crucial pathological factor in the development of urolithiasis, and *B. ligulata* exhibits pronounced antioxidant activity that significantly contributes to its renoprotective effect. Experimental studies have demonstrated that treatment with *B. ligulata* extract significantly decreases malondialdehyde levels while enhancing the activities of endogenous antioxidant enzymes such as superoxide dismutase, catalase, and

glutathione peroxidase in renal tissues. By suppressing oxalate-induced oxidative injury, the plant prevents epithelial cell damage and the subsequent exposure of crystal-binding sites that facilitate crystal adherence and retention [91]. The anti-inflammatory activity of *B. ligulata* also plays an important role in its antiurolithiatic mechanism. Renal inflammation promotes crystal retention and recurrence of stone formation. The plant extract has been shown to significantly reduce inflammatory mediators, including cyclooxygenase-2, prostaglandins, and pro-inflammatory cytokines, in experimental models of renal injury [92]. This anti-inflammatory property limits crystal-induced tubular damage and fibrosis, thereby creating an unfavorable environment for stone persistence and growth. From an ethnomedicinal perspective, *B. ligulata* occupies a prominent position in traditional medicine for urinary stone disorders. It is a key ingredient in several classical Ayurvedic formulations such as Pashanbhedadi Kwatha and Varunadi Kwatha, which are widely prescribed for the management of urolithiasis and related urinary ailments [93]. The continued use of *B. ligulata* in traditional clinical practice, combined with its strong experimental validation, highlights its therapeutic reliability and pharmacological relevance. In recent years, limited clinical investigations have also supported the antiurolithiatic efficacy of *B. ligulata*. Patients receiving formulations containing *B. ligulata* have shown significant improvement in urinary symptoms, reduction in stone size, and decreased recurrence rates without major adverse effects. However, large-scale randomized controlled trials remain scarce, and further clinical validation is required to establish standardized dosing protocols and long-term safety.

Phyllanthus niruri

Phyllanthus niruri L. (family Phyllanthaceae), commonly known as stone breaker, Chanca piedra, or Bhumi amla, is one of the most extensively investigated traditional medicinal plants for the management and prevention of urolithiasis. The plant has a long history of ethnomedicinal use in Ayurveda, Siddha, Traditional Chinese Medicine, and Amazonian folk medicine for the treatment of kidney stones, urinary tract infections, and hepatobiliary disorders. The whole plant is traditionally employed in the form of decoctions, infusions, and powders for

promoting stone disintegration and preventing recurrence. Its widespread traditional usage has stimulated extensive pharmacological and clinical research to validate its antiurolithiatic potential. Phytochemical investigations of *P. niruri* have revealed the presence of several biologically active constituents, including lignans such as phyllanthin and hypophyllanthin, flavonoids, tannins, alkaloids, terpenoids, and polyphenolic compounds. These constituents exhibit strong antioxidant, anti-inflammatory, and diuretic properties that collectively contribute to the plant's antiurolithiatic activity [94]. The synergistic interaction among these phytochemicals is considered responsible for the broad-spectrum pharmacological effects observed with *P. niruri*. Experimental studies have provided compelling evidence for the inhibitory effect of *P. niruri* on stone formation. In ethylene glycol-induced hyperoxaluric rat models, administration of aqueous and alcoholic extracts of *P. niruri* significantly reduced urinary oxalate, calcium, and phosphate excretion while increasing urinary magnesium and citrate levels. These biochemical alterations were associated with a marked reduction in renal calcium oxalate crystal deposition. Histopathological analysis further confirmed preservation of normal renal architecture, with a significant decrease in tubular necrosis, epithelial desquamation, and interstitial inflammation in treated animals. In vitro crystallization studies have demonstrated that *P. niruri* exhibits a potent inhibitory effect on calcium oxalate nucleation, crystal growth, and aggregation. The extract has been shown to interfere with crystal-crystal and crystal-cell interactions, leading to reduced formation of calcium oxalate monohydrate crystals, which are considered the most pathogenic form due to their high adhesive properties [95]. The ability of *P. niruri* to alter crystal morphology and reduce crystal size facilitates their easy elimination through urine and prevents their retention within renal tubules. Clinical investigations have also supported the role of *P. niruri* in preventing stone recurrence. In patients with recurrent calcium oxalate urolithiasis, prolonged administration of *P. niruri* extract resulted in a significant reduction in stone recurrence rates and improvement in urinary biochemical parameters. Ultrasound evaluations demonstrated inhibition of new stone formation and gradual reduction in the size of pre-existing microcalculi. The plant was well

tolerated, with minimal gastrointestinal discomfort reported in a small number of patients, indicating a favorable safety profile for long-term use. Mechanistic studies have revealed that one of the primary modes of action of *P. niruri* is its strong antioxidant activity. Oxalate-induced oxidative stress plays a pivotal role in renal epithelial injury and crystal adhesion. *P. niruri* extract has been shown to significantly decrease lipid peroxidation and restore endogenous antioxidant enzyme levels, including superoxide dismutase, catalase, and glutathione peroxidase in renal tissue [96]. By reducing oxidative damage, the plant prevents epithelial injury and limits the exposure of crystal-binding molecules that facilitate crystal retention. Another important mechanism contributing to the antiurolithiatic effect of *P. niruri* is its diuretic activity. Increased urine flow reduces urinary supersaturation of lithogenic solutes and mechanically flushes out microcrystals before they undergo aggregation and growth [97]. Additionally, the plant modulates urinary pH and inhibits hepatic oxalate synthesis, further reducing the availability of oxalate for stone formation. Anti-inflammatory activity also plays a significant role in the therapeutic action of *P. niruri*. Experimental studies have demonstrated that extracts of the plant significantly suppress the expression of inflammatory mediators such as tumor necrosis factor- α , interleukin-6, and cyclooxygenase-2 in renal tissue during hyperoxaluric conditions [98]. By attenuating crystal-induced inflammatory responses, the plant reduces tubular injury, fibrosis, and recurrence of stone formation. Collectively, the available experimental and clinical evidence strongly supports the efficacy of *Phyllanthus niruri* in inhibiting stone formation and reducing the recurrence of urolithiasis. Its multitargeted mechanisms, including inhibition of crystal nucleation and aggregation, modulation of urinary biochemistry, antioxidant and anti-inflammatory actions, and diuretic effect, provide a robust scientific justification for its traditional use as a natural lithotriptic agent. Despite promising outcomes, further large-scale randomized controlled trials are necessary to establish standardized dosage regimens and confirm its long-term clinical efficacy [99].

Boerhaaviadiffusa

Boerhaavia diffusa L. (family Nyctaginaceae), commonly known as Punarnava, is a highly valued medicinal plant in Ayurveda, Unani, and various indigenous systems of medicine for the treatment of renal and urinary disorders, including urolithiasis. The whole plant and roots are traditionally used for their diuretic, anti-inflammatory, and nephroprotective properties. The Sanskrit name “Punarnava,” meaning “renewer of the body,” reflects its classical use as a rejuvenating agent in chronic kidney diseases and urinary tract ailments. Its widespread ethnomedicinal application in the management of urinary calculi has stimulated extensive experimental research to validate its therapeutic potential [100]. Phytochemical investigations of *B. diffusa* have revealed a broad spectrum of bioactive constituents, including rotenoids such as boeravinones (A–F), flavonoids, alkaloids, lignans, triterpenoids, steroids, and glycosides. Among these, boeravinones have been identified as the principal compounds responsible for the plant’s diuretic and antiurolithiatic activities. The synergistic interaction of these phytochemicals confers multiple pharmacological effects that are relevant to the prevention and management of urolithiasis. Experimental studies have consistently demonstrated the antiurolithiatic potential of *B. diffusa* in animal models. In ethylene glycol-induced hyperoxaluric rats, administration of aqueous and alcoholic extracts of *B. diffusa* resulted in a significant reduction in urinary oxalate, calcium, and phosphate levels, along with a marked increase in urinary magnesium concentration. These biochemical changes were associated with a substantial decrease in renal calcium oxalate crystal deposition. Histopathological examination of renal tissue from treated animals revealed significant protection against tubular degeneration, epithelial necrosis, and interstitial inflammation compared with untreated controls. In vitro crystallization studies have further substantiated the direct crystal-inhibitory action of *B. diffusa*. The plant extract has been shown to significantly inhibit calcium oxalate nucleation and aggregation in a concentration-dependent manner. The suppression of crystal growth is believed to occur through chelation of free calcium ions and adsorption of phytoconstituents on the crystal surface, thereby preventing further ionic deposition and crystal enlargement [101]. This direct interference with the

physicochemical processes of crystallization provides a mechanistic explanation for its traditional litholytic reputation. The pronounced diuretic activity of *B. diffusa* plays a central role in its antiurolithiatic mechanism. Experimental studies have demonstrated that administration of the plant extract significantly increases urine volume and electrolyte excretion without causing electrolyte imbalance [120]. Enhanced urine flow reduces urinary supersaturation of lithogenic substances such as calcium and oxalate and facilitates the mechanical flushing of microcrystals from the renal tubules and urinary tract, thereby preventing their retention and subsequent growth. Oxidative stress is a critical pathogenic factor in calcium oxalate stone formation, and *B. diffusa* exhibits strong antioxidant activity that contributes to its renoprotective effect. Treatment with *B. diffusa* extract has been shown to significantly decrease lipid peroxidation and restore antioxidant enzyme activities, including superoxide dismutase, catalase, and reduced glutathione in renal tissue [102]. By attenuating oxalate-induced oxidative injury, the plant preserves renal epithelial integrity and reduces the availability of crystal-binding sites that promote crystal adherence. In addition to its antioxidant action, *B. diffusa* exhibits potent anti-inflammatory activity that further enhances its antiurolithiatic efficacy. In experimental models of renal injury, the plant extract significantly suppressed the expression of pro-inflammatory mediators such as tumor necrosis factor- α , interleukin-1 β , and cyclooxygenase-2 [103]. The reduction of inflammation limits tubular injury, leukocyte infiltration, and fibrotic changes, thereby creating an unfavorable microenvironment for crystal retention and recurrent stone formation. Although clinical studies on the antiurolithiatic efficacy of *B. diffusa* remain relatively limited, its inclusion in several traditional polyherbal formulations prescribed for urolithiasis provides indirect clinical support for its therapeutic role. Preliminary clinical observations have reported improvement in urinary symptoms, reduction in stone size, and decreased recurrence following administration of Punarnava-based formulations, with minimal adverse effects. However, well-designed randomized controlled trials are still required to establish definitive clinical efficacy, optimal dosage, and long-term safety.

Didymocarpospedicellata

Didymocarpus pedicellata R. Br. (family Gesneriaceae), commonly known as Patharchatta or Shilapushpa, is an important lithotriptic medicinal plant extensively used in Ayurveda and traditional systems of medicine for the management of urolithiasis and other urinary tract disorders. The whole plant, particularly the aerial parts, is traditionally administered in the form of decoctions and powders for dissolving urinary calculi and promoting diuresis. The plant is a key ingredient of several classical polyherbal formulations, most notably the well-known Ayurvedic formulation Cystone, which is widely prescribed for kidney stone disease. The consistent ethnomedicinal use of *D. pedicellata* as a stone-dissolving agent has led to its extensive pharmacological evaluation. Phytochemical investigations have demonstrated that *D. pedicellata* contains a wide range of bioactive constituents, including flavonoids, phenolic acids, tannins, glycosides, saponins, sterols, and terpenoids. These compounds are known to exert antioxidant, anti-inflammatory, and crystallization-modulating activities, which collectively contribute to the antiurolithiatic potential of the plant [104]. The high phenolic and flavonoid content of the plant is particularly associated with its strong antioxidant and renoprotective properties. The antiurolithiatic activity of *D. pedicellata* has been substantiated through several experimental studies using ethylene glycol-induced hyperoxaluric rat models. Oral administration of aqueous and alcoholic extracts of the plant resulted in a significant reduction in urinary excretion of calcium, oxalate, and phosphate, along with a concomitant increase in urinary magnesium levels [105]. These changes were associated with a marked decrease in renal crystal deposition. Histopathological examination of renal tissue from treated animals revealed substantial protection against tubular necrosis, epithelial desquamation, and interstitial inflammation compared with untreated hyperoxaluric controls. In vitro crystallization assays have demonstrated that *D. pedicellata* extract significantly inhibits calcium oxalate nucleation, crystal growth, and aggregation in a concentration-dependent manner. The extract alters crystal morphology and reduces the formation of the highly adhesive calcium oxalate monohydrate crystals, thereby facilitating the elimination of smaller, less pathogenic crystal forms through urine [106]. This

direct interference with the physicochemical stages of stone formation provides a mechanistic explanation for its traditional lithotriptic activity. Oxidative stress plays a central role in the pathogenesis of urolithiasis by promoting renal epithelial injury and crystal retention. *D. pedicellata* exhibits strong antioxidant activity, as evidenced by significant reductions in lipid peroxidation and restoration of endogenous antioxidant enzymes such as superoxide dismutase, catalase, and glutathione peroxidase in renal tissues of hyperoxaluric animals [107]. By attenuating oxalate-induced oxidative damage, the plant preserves epithelial integrity and limits the exposure of molecular sites responsible for crystal adhesion and retention. The anti-inflammatory activity of *D. pedicellata* further contributes to its antiurolithiatic efficacy. Crystal-induced renal injury is accompanied by activation of inflammatory mediators that exacerbate tubular damage and promote fibrosis. Experimental studies have shown that treatment with *D. pedicellata* significantly suppresses the expression of pro-inflammatory cytokines, including tumor necrosis factor- α and interleukin- 1β , as well as cyclooxygenase-2 activity in renal tissue [108]. This anti-inflammatory effect limits progressive renal injury and reduces the likelihood of recurrent stone formation. The diuretic activity of *D. pedicellata* also plays a crucial role in its therapeutic effect. Increased urine output reduces urinary supersaturation of lithogenic solutes and mechanically facilitates the expulsion of microcrystals from the urinary tract. Experimental evaluations have demonstrated that the plant extract significantly increases urine volume and electrolyte excretion without producing adverse electrolyte imbalance, thereby supporting its traditional use as a safe diuretic agent [109]. Clinical evidence for the antiurolithiatic efficacy of *D. pedicellata* is primarily derived from studies conducted on polyherbal formulations in which it is a principal ingredient. Clinical observations in patients with recurrent urolithiasis treated with formulations containing *D. pedicellata* have shown significant reduction in stone size, improvement in urinary symptoms, and decreased recurrence rates without significant adverse effects [110]. However, clinical trials evaluating *D. pedicellata* as a single agent remain limited, and further controlled studies are required to establish its independent therapeutic efficacy.

Other promising plants (e.g., *Aerva lanata*, *Cynodon dactylon*, *Hibiscus sabdariffa*, *Ammi visnaga*)

In addition to the well-established antiurolithiatic plants discussed previously, several other traditional medicinal plants have demonstrated significant promise for the pharmacological management of urolithiasis. Among these, *Aerva lanata*, *Cynodon dactylon*, *Hibiscus sabdariffa*, and *Ammi visnaga* have attracted considerable scientific attention due to their strong ethnomedicinal background and increasing experimental validation.

Aerva lanata (L.) Juss. ex Schult. (family Amaranthaceae), commonly known as Mountain knotgrass, is extensively used in Ayurveda and Siddha medicine as a diuretic and litholytic agent. The whole plant is traditionally employed for the treatment of urinary calculi, dysuria, and cystitis. Phytochemical investigations have revealed the presence of flavonoids, alkaloids, terpenoids, tannins, and saponins, which collectively contribute to its antiurolithiatic activity [111]. Experimental studies in ethylene glycol-induced hyperoxaluric rats have demonstrated that *A. lanata* significantly reduces urinary calcium, oxalate, and phosphate levels while increasing magnesium excretion. These biochemical changes were associated with a marked reduction in renal calcium oxalate crystal deposition and preservation of normal renal histoarchitecture. The antiurolithiatic mechanism of *A. lanata* is attributed to its strong diuretic activity, inhibition of crystal nucleation and aggregation, antioxidant defense against oxalate-induced oxidative injury, and suppression of renal inflammation [112].

Cynodon dactylon (L.) Pers. (family Poaceae), commonly known as Bermuda grass or Durva, is widely used in traditional Indian medicine for the treatment of urinary disorders, including urolithiasis. The plant contains bioactive constituents such as flavonoids, alkaloids, glycosides, triterpenoids, and minerals. In vivo studies have demonstrated that aqueous extracts of *C. dactylon* significantly inhibit the formation of calcium oxalate stones in experimental rat models by reducing urinary concentrations of lithogenic ions. The plant also exhibits pronounced diuretic activity, which enhances urine flow and facilitates the elimination of

microcrystals. Furthermore, its antioxidant properties reduce lipid peroxidation and protect renal epithelial cells from oxalate-induced injury, thereby limiting crystal retention [113].

Hibiscus sabdariffa L. (family Malvaceae), commonly known as Roselle, is traditionally consumed as a medicinal beverage for the treatment of hypertension, liver disorders, and urinary tract diseases. The calyces of the plant are rich in anthocyanins, flavonoids, organic acids, and polyphenols that exhibit strong antioxidant and diuretic properties. Experimental studies have demonstrated that *H. sabdariffa* extract significantly reduces calcium oxalate crystal formation and deposition in rat models of hyperoxaluria. The antiurolithiatic activity of the plant is mediated through modulation of urinary pH, enhancement of citrate excretion, inhibition of crystal aggregation, and suppression of oxidative stress-induced renal epithelial damage. Additionally, the antimicrobial effect of *H. sabdariffa* may contribute to the prevention of infection-related stones [114].

Ammi visnaga (L.) Lam. (family Apiaceae), commonly known as Khella, has a long history of traditional use in Mediterranean and Middle Eastern medicine for urinary calculi and ureteral spasms. The fruits of the plant contain potent furanochromones, primarily khellin and visnagin, which exhibit smooth muscle relaxant, diuretic, and litholytic properties. Experimental studies have shown that *A. visnaga* extract promotes the relaxation of ureteral smooth muscle, facilitating the expulsion of small calculi and preventing urinary obstruction. Additionally, the plant has been shown to inhibit calcium oxalate crystal growth and reduce renal crystal deposition in hyperoxaluric animal models. Its antioxidant and anti-inflammatory activities further contribute to renal protection and suppression of crystal-induced tubular injury.

Collectively, these plants exhibit significant antiurolithiatic activity through multiple complementary mechanisms, including inhibition of crystal nucleation and aggregation, enhancement of diuresis, modulation of urinary biochemical parameters, antioxidant protection of renal epithelium, and attenuation of renal inflammation. Although substantial experimental evidence supports

their therapeutic potential, large-scale controlled clinical trials remain limited. Further investigation is required to establish standardized extracts, optimal dosing regimens, and long-term safety profiles before their widespread clinical adoption in evidence-based phytotherapy for urolithiasis.

6. Experimental Models Used in Evaluating Anti-Urolithiatic Activity

In vitro Models

In vitro experimental models constitute the primary screening tools for the rapid and mechanistic evaluation of anti-urolithiatic potential of medicinal plant extracts, isolated phytoconstituents, and synthetic compounds. These models simulate the physicochemical events of renal stone formation under controlled laboratory conditions and provide valuable insights into the effects of test agents on crystal nucleation, growth, aggregation, and dissolution. Owing to their simplicity, reproducibility, cost-effectiveness, and ethical advantages over in vivo experiments, in vitro assays remain indispensable in the early stages of antiurolithiatic drug discovery. Crystal nucleation assays are widely employed to examine the ability of plant extracts to inhibit the initial formation of calcium oxalate crystals from supersaturated solutions of calcium and oxalate ions. These assays are typically conducted using metastable solutions in which crystal formation is monitored spectrophotometrically or turbidimetrically by measuring changes in optical density over time. A delay in the onset of turbidity or a reduction in the rate of nucleation in the presence of test samples is considered indicative of nucleation inhibitory activity. Several medicinal plant extracts, including *Bergenia ligulata*, *Phyllanthus niruri*, and *Aerva lanata*, have demonstrated significant inhibition of calcium oxalate nucleation in such models, thereby suggesting their potential role in preventing the earliest stage of stone formation [115]. These assays also allow dose-dependent assessment and comparative evaluation of plant extracts with standard inhibitors such as citrate. Crystal aggregation tests evaluate the capacity of test agents to prevent the clumping of pre-formed calcium oxalate microcrystals into larger aggregates capable of renal retention. In these models, freshly prepared crystals are suspended in physiological buffers and incubated

with or without plant extracts, followed by spectrophotometric or microscopic analysis of aggregate size and number. Aggregation is a critical step in stone pathogenesis because small crystals are generally excreted in urine, whereas larger aggregates tend to become lodged within renal tubules. Numerous phytoconstituent-rich extracts have been shown to significantly inhibit aggregation by altering crystal surface charge, reducing interparticle adhesion, and modulating ionic interactions [116]. Polyphenols, saponins, and polysaccharides present in many antiurolithiatic plants are believed to adsorb onto the crystal surface and prevent crystal–crystal interaction. Crystal dissolution methods are employed to assess the ability of test substances to dissolve pre-formed urinary calculi or laboratory-generated calcium oxalate crystals. These studies typically involve incubation of authentic human kidney stones or synthetic calcium oxalate in buffer solutions containing plant extracts under physiological pH and temperature conditions. The extent of dissolution is determined by measuring changes in stone weight, ionic concentration in solution, or optical density over time. Several traditional medicinal plants, including *Ammi visnaga*, *Bergenia ligulata*, and *Boerhaavia diffusa*, have demonstrated significant litholytic activity in vitro through gradual dissolution of calcium oxalate and phosphate stones [117]. The dissolution effect is attributed to the chelating properties of organic acids, phenolics, and other weak acids that form soluble complexes with calcium ions. Collectively, in vitro models offer critical mechanistic evidence for the antiurolithiatic activity of medicinal plants by enabling the direct evaluation of their effects on crystal formation dynamics. However, these models do not fully replicate the complex biological environment of the kidney, where factors such as urinary macromolecules, renal epithelial interactions, oxidative stress, and inflammation significantly influence stone development. Therefore, in vitro findings must be carefully interpreted and subsequently validated using appropriate in vivo experimental models for reliable translational application [118].

In vivo Models

In vivo experimental models are essential for the comprehensive pharmacological evaluation of anti-urolithiatic agents, as they closely simulate the

complex biochemical, metabolic, and pathological events involved in human stone formation. These models allow the investigation of not only crystal formation and renal deposition but also the influence of oxidative stress, inflammation, renal function, and systemic metabolic alterations. Among the various experimental approaches, chemically induced hyperoxaluric models using ethylene glycol, ammonium oxalate, and sodium oxalate are the most widely employed for screening the anti-urolithiatic potential of traditional medicinal plants. The ethylene glycol-induced urolithiasis model is considered the gold standard for evaluating anti-urolithiatic activity in rodents. Chronic administration of ethylene glycol in drinking water leads to its hepatic metabolism into glycolic and oxalic acids, resulting in sustained hyperoxaluria and subsequent deposition of calcium oxalate crystals in renal tissues. This model reliably reproduces the biochemical and histopathological features of human nephrolithiasis, including tubular crystal retention, oxidative stress, and renal epithelial injury. Numerous studies have utilized this model to validate the efficacy of plants such as *Tribulus terrestris*, *Phyllanthus niruri*, *Boerhaavia diffusa*, and *Bergenia ligulata*, demonstrating significant reductions in urinary oxalate, calcium, and phosphate excretion, along with decreased renal crystal deposition [119]. The reversibility of stone formation in curative protocols further enables the assessment of litholytic and nephroprotective properties of plant extracts. Ammonium oxalate-induced models are commonly employed for the acute induction of hyperoxaluria and rapid formation of calcium oxalate crystals. Oral or intraperitoneal administration of ammonium oxalate leads to sudden elevation of oxalate levels in plasma and urine, causing extensive renal tubular supersaturation and crystal precipitation. This model is particularly useful for evaluating the prophylactic efficacy of anti-urolithiatic agents and their ability to prevent early stages of nucleation and aggregation. Experimental studies using ammonium oxalate have demonstrated that various medicinal plant extracts significantly reduce crystal load and maintain normal renal architecture by modulating lithogenic risk factors [120]. Sodium oxalate-induced urolithiasis is another acute experimental model used to investigate the early biochemical and oxidative consequences of oxalate overload. Parenteral administration of sodium oxalate produces rapid

hyperoxalemia and oxidative stress within renal tissues, leading to lipid peroxidation, mitochondrial dysfunction, and epithelial injury, which collectively promote crystal adherence and retention. This model is particularly useful for mechanistic studies evaluating antioxidant and cytoprotective properties of plant-derived compounds. Several studies have shown that antioxidant-rich medicinal plants mitigate oxalate-induced renal damage by restoring endogenous antioxidant enzymes such as superoxide dismutase, catalase, and glutathione peroxidase [121]. Rats and mice serve as the principal experimental animals for in vivo urolithiasis research due to their genetic stability, ease of handling, well-characterized renal physiology, and strong reproducibility of stone formation. Wistar and Sprague–Dawley rats are the most frequently used species, although Swiss albino mice have also been utilized for mechanistic and genetic investigations. These models allow detailed evaluation of urinary biochemical parameters, including calcium, oxalate, phosphate, magnesium, uric acid, and citrate levels, which directly reflect lithogenic risk. In addition, serum creatinine and blood urea nitrogen levels provide important information regarding renal functional integrity during stone development and therapeutic intervention. Oxidative stress and inflammatory biomarkers are now recognized as critical endpoints in in vivo anti-urolithiatic studies. Oxalate-induced crystal deposition is strongly associated with increased generation of reactive oxygen species, lipid peroxidation, and depletion of endogenous antioxidant defenses within renal tissues. Malondialdehyde, reduced glutathione, superoxide dismutase, catalase, and nitric oxide are routinely measured to assess oxidative stress status. Simultaneously, inflammatory mediators such as tumor necrosis factor- α , interleukin-1 β , cyclooxygenase-2, and nuclear factor- κ B are evaluated to understand the inflammatory cascade triggered by crystal–epithelium interactions. Numerous medicinal plant extracts have demonstrated significant attenuation of oxidative stress and inflammatory signaling in hyperoxaluric animal models, thereby preventing tubular damage and subsequent crystal retention. Overall, in vivo models provide a comprehensive platform for evaluating the preventive, curative, nephroprotective, antioxidant, and anti-inflammatory effects of

traditional medicinal plants against urolithiasis. These models bridge the gap between in vitro observations and clinical relevance by incorporating systemic metabolism, renal excretory function, and pathophysiological complexity. However, despite their high translational value, careful standardization of induction protocols, treatment duration, and biomarker evaluation is essential for generating reproducible and clinically meaningful data [122].

Ex vivo and computational approaches

Beyond in vitro and in vivo models, ex vivo and computational approaches have emerged as valuable tools for evaluating the anti-urolithiatic potential of traditional medicinal plants. Ex vivo models utilize excised renal tissues, urine samples, or isolated renal epithelial cells to investigate the direct interaction of plant extracts and phytochemicals with crystal formation, adhesion, and renal cellular mechanisms. These models provide a more physiologically relevant environment compared with conventional in vitro assays, allowing examination of tissue-specific responses under controlled experimental conditions. Renal tissue assays, a widely employed ex vivo approach, involve incubation of isolated kidney slices or tubular epithelial cells with supersaturated solutions of calcium oxalate in the presence or absence of plant extracts. This methodology enables detailed assessment of crystal adherence, internalization, and retention within renal tissue. Studies using *Bergenia ligulata* and *Phyllanthus niruri* have demonstrated that their extracts significantly reduce crystal attachment to renal epithelial surfaces, prevent intracellular oxalate accumulation, and mitigate crystal-induced cytotoxicity. Additionally, ex vivo renal models allow evaluation of oxidative stress markers and inflammatory mediators at the tissue level, providing insights into the protective mechanisms of phytoconstituents against crystal-induced nephrotoxicity. Computational approaches, particularly molecular docking and in silico simulations, have increasingly complemented experimental studies by predicting the interaction of bioactive phytochemicals with key molecular targets involved in urolithiasis. Molecular docking studies assess the binding affinity and mode of interaction of phytoconstituents with proteins implicated in stone formation, such as calcium-binding proteins, oxalate

transporters, and crystallization modulators. For instance, in silico analysis of lignans from *Phyllanthus niruri* and flavonoids from *Aerva lanata* revealed high binding affinity to calcium oxalate crystals and crystal-associated proteins, suggesting potential mechanisms for inhibition of nucleation, growth, and aggregation [123]. These computational predictions enable the rational selection of candidate compounds for further in vitro and in vivo validation, thereby optimizing resource utilization and accelerating the drug discovery process. Ex vivo and computational approaches also facilitate the identification of synergistic interactions among phytochemicals within polyherbal formulations. By combining tissue-based assays with molecular docking, researchers can elucidate the contributions of individual compounds to the overall antiurolithiatic activity. This integrative methodology provides mechanistic insights at both molecular and tissue levels, bridging the gap between empirical ethnomedicinal knowledge and modern pharmacological understanding. Collectively, ex vivo renal tissue assays and computational molecular docking approaches offer powerful complementary tools for evaluating the antiurolithiatic activity of traditional medicinal plants. They allow mechanistic dissection of crystal–cell interactions, prediction of bioactive compound efficacy, and optimization of phytotherapeutic interventions. When used in combination with in vitro and in vivo models, these methodologies provide a comprehensive framework for the systematic investigation of plant-based antiurolithiatic agents, guiding the development of effective and safe phytopharmaceuticals [124].

7. Clinical Evidence and Human Studies

Clinical evaluation of traditional medicinal plants for urolithiasis is pivotal for translating preclinical findings into safe and effective therapeutic interventions in humans. Over the past two decades, several clinical studies have investigated the efficacy of both single-plant extracts and polyherbal formulations in the management of kidney stones, focusing on stone dissolution, prevention of recurrence, improvement of urinary biochemical parameters, and overall safety. A substantial body of clinical evidence supports the efficacy of *Phyllanthus niruri*, a widely studied litholytic agent. Randomized and open-label studies have demonstrated that oral

administration of aqueous or ethanolic extracts of *P. niruri* significantly facilitates the reduction in stone size and, in some cases, complete expulsion of small renal calculi. The mechanism is postulated to involve modulation of urinary calcium and oxalate concentrations, enhancement of citrate excretion, inhibition of crystal nucleation, and protection of renal epithelial integrity. Across these studies, *P. niruri* was generally well tolerated, with no serious adverse events reported, reinforcing its favorable safety profile. Polyherbal formulations, particularly standardized Ayurvedic preparations, have also been extensively evaluated in clinical settings. Cystone®, containing *Didymocarpus pedicellata*, *Bergenia ligulata*, *Shilapushpa*, and other medicinal plants, is one of the most studied formulations. Multicenter clinical trials involving patients with radiologically confirmed nephrolithiasis demonstrated significant reductions in stone size and number, alongside improvements in urinary biochemistry, including calcium, oxalate, uric acid, and magnesium levels. The formulation exhibited both litholytic and prophylactic effects, decreasing the risk of recurrent stone formation over prolonged administration. Other formulations incorporating *Boerhaavia diffusa*, *Aerva lanata*, and *Hibiscus sabdariffa* have also been observed to alleviate stone-associated symptoms, reduce urinary supersaturation of lithogenic ions, and support renal function in patients with recurrent stones [125]. Despite the encouraging results, several limitations of existing clinical evidence must be acknowledged. Most studies have relatively small sample sizes, short treatment durations, or lack placebo-controlled, double-blind designs, limiting the robustness and generalizability of conclusions. Variability in plant sources, preparation methods, and dosing regimens further complicates standardization. Additionally, long-term safety data are sparse, and potential interactions with conventional pharmacological therapies for urolithiasis have not been systematically studied. Nonetheless, reported studies consistently indicate that these plant-based therapies are generally well tolerated, with minimal adverse effects, primarily mild gastrointestinal disturbances.

8.Toxicity, Safety, And Standardization Issues

The increasing clinical and preclinical utilization of traditional medicinal plants for urolithiasis

necessitates careful consideration of their safety, toxicity, and standardization. While ethnomedicinal experience and clinical studies suggest a generally favorable safety profile, systematic evaluation of toxicological parameters and rigorous quality control remain essential to ensure reproducible efficacy and minimize adverse effects. Several key antiurolithiatic plants, including *Phyllanthus niruri*, *Bergenia ligulata*, *Boerhaavia diffusa*, *Tribulus terrestris*, and *Aerva lanata*, have undergone preliminary toxicological assessment in both animal models and human studies. Acute and subacute toxicity studies in rodents have demonstrated high safety margins, with no significant mortality or organ toxicity observed at doses several-fold higher than therapeutic levels. For instance, oral administration of *Phyllanthus niruri* extracts up to 5 g/kg in rats did not elicit significant behavioral, hematological, or histopathological abnormalities. Similarly, *Bergenia ligulata* and *Boerhaavia diffusa* have been shown to be non-toxic in standard acute toxicity assays, supporting their safe use in humans. However, chronic toxicity studies are limited, and the long-term effects of continuous administration, particularly in populations with comorbidities such as renal impairment, have not been comprehensively characterized. Dose standardization presents a major challenge in clinical translation due to variations in plant species, growth conditions, harvesting methods, and extraction techniques. These factors contribute to significant variability in the concentration and composition of active phytochemicals, which directly affects pharmacological efficacy. For example, the content of bergenin in *Bergenia ligulata* and the flavonoid fraction in *Aerva lanata* can vary substantially depending on geographical origin and processing methods. Consequently, establishing reproducible therapeutic doses requires meticulous standardization of raw material, extraction procedures, and quantification of bioactive constituents through validated analytical methods such as high-performance liquid chromatography (HPLC) and mass spectrometry. Quality control of medicinal plant preparations is further complicated by adulteration, contamination with heavy metals, pesticides, microbial pathogens, and variability in secondary metabolite content. Regulatory guidelines increasingly emphasize the need for Good Agricultural and Collection Practices (GACP) and

Good Manufacturing Practices (GMP) to ensure batch-to-batch consistency, safety, and efficacy of herbal formulations [126]. Phytochemical fingerprinting and marker-based standardization are recommended strategies for achieving quality control and minimizing variability in clinical outcomes. Herb–drug interactions are an additional concern, particularly when plant-based therapies are used concomitantly with conventional pharmacological agents such as thiazide diuretics, potassium citrate, allopurinol, or nonsteroidal anti-inflammatory drugs. Some phytochemicals may alter drug metabolism through modulation of cytochrome P450 enzymes or drug transporters, potentially affecting plasma concentrations and therapeutic efficacy. Although clinical studies of commonly used antiurolithiatic plants have not reported significant herb–drug interactions, systematic pharmacokinetic studies remain limited, highlighting the importance of monitoring and caution in patients receiving concurrent therapy.

CHALLENGES, GAPS, AND FUTURE RESEARCH DIRECTIONS

Despite the substantial evidence supporting the antiurolithiatic potential of traditional medicinal plants, several challenges and knowledge gaps hinder their full integration into contemporary nephrolithiasis management. A critical limitation is the paucity of detailed mechanistic studies elucidating the precise molecular pathways through which plant extracts and phytochemicals exert their litholytic, crystallization-inhibitory, antioxidant, and anti-inflammatory effects. Although preclinical studies indicate roles for diuretic action, inhibition of crystal nucleation and aggregation, and oxidative stress mitigation, the involvement of specific molecular targets, signaling pathways, and renal transporters remains poorly characterized. Mechanistic investigations using molecular biology techniques, ex vivo renal models, and computational approaches are essential to bridge this gap and enhance rational drug development. The lack of standardized extracts and well-defined phytochemical content further constrains reproducibility and clinical translation. Variability in plant species, growth conditions, harvesting, extraction methods, and bioactive component concentrations leads to inconsistent pharmacological outcomes. The absence of universal

standardization protocols limits the ability to compare results across studies and undermines regulatory acceptance. Future research should prioritize the development of standardized, chemically characterized extracts with validated bioactive markers to ensure consistent efficacy and safety. Another significant gap is the limited number and scale of rigorously conducted clinical trials. While several small-scale, open-label, and observational studies suggest favorable outcomes, large randomized controlled trials are scarce. Insufficient clinical evidence hampers the formulation of evidence-based guidelines, dosing recommendations, and long-term safety profiles. There is a pressing need for multicenter trials with standardized interventions, appropriate controls, and long-term follow-up to confirm both efficacy and safety in diverse patient populations. The potential for synergistic plant combinations remains underexplored. Traditional polyherbal formulations often combine multiple species to achieve complementary therapeutic effects, including enhanced litholytic activity, antioxidant protection, and diuresis. Systematic studies investigating additive or synergistic interactions among phytochemicals are necessary to optimize multi-component formulations and rationalize their use in clinical practice. Advanced analytical tools and bioassays can facilitate the identification of synergistic combinations that maximize efficacy while minimizing toxicity [128]. Modern technologies offer promising avenues to overcome these challenges and accelerate the development of plant-based antiurolithiatic therapies. Metabolomics can provide comprehensive profiling of bioactive constituents and their metabolic fate, elucidating mechanisms of action. Network pharmacology approaches can integrate molecular, cellular, and systemic interactions to predict potential targets and pathways affected by complex herbal extracts. Nanotechnology-enhanced herbal formulations, such as nanoparticle-encapsulated plant extracts, may improve bioavailability, targeted delivery, and therapeutic efficacy while reducing required doses and systemic side effects. Integration of these technologies into future research strategies can enhance mechanistic understanding, standardization, and clinical translation of traditional medicinal plants [129].

CONCLUSION

Traditional medicinal plants represent a scientifically validated and clinically promising approach for the long-term management of urolithiasis. Their therapeutic efficacy stems from the synergistic action of diverse phytochemicals that target multiple stages of stone formation. These bioactive compounds effectively inhibit calcium oxalate nucleation, crystal growth, and aggregation while simultaneously enhancing diuresis, modulating urinary biochemistry, and promoting the dissolution and expulsion of microcrystals. Additionally, their strong antioxidant and anti-inflammatory properties protect renal epithelial cells from oxalate-induced oxidative stress and tissue injury, thereby minimizing crystal adherence and preventing recurrence. Experimental studies using validated in vitro, in vivo, and ex vivo models consistently demonstrate the ability of plants such as *Phyllanthus niruri*, *Bergenia ligulata*, *Tribulus terrestris*, *Boerhaavia diffusa*, and *Crataeva nurvala* to significantly reduce stone burden and restore renal function. Early clinical findings further support their safety, tolerability, and potential to reduce recurrence rates in patients with calcium oxalate stones. However, challenges remain regarding standardization of plant extracts, identification of active phytoconstituents, optimization of dosage, and rigorous evaluation through large-scale randomized controlled trials. Overall, traditional medicinal plants provide a cost-effective, safe, and holistic phytotherapeutic alternative to conventional therapies. Continued scientific exploration and clinical validation will be essential to fully integrate these botanicals into evidence-based management strategies for urolithiasis.

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