

REVIEW

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The role of plant-derived compounds in the management and prevention of urolithiasis: a review of evidence and mechanisms

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Abstract

Urolithiasis, the condition of forming stones in the urinary system, is a common health problem worldwide and tends to recur. Pathophysiology includes stages such as supersaturation, nucleation, growth, aggregation, and crystal-cell interactions. Most conventional treatments have disadvantages of failing to prevent recurrence and often with side effects. This review has discussed the therapeutic potential of some Sri Lankan dietary and medicinal plants in the management and prevention of urolithiasis. Dietary plants such as *Annona muricata* L., *Manilkara zapota* (L.) P. Royen, *Garcinia cambogia* (Gaertn.) Desr., *Camellia sinensis* (L.) Kuntze, and *Punica granatum* L. exhibit properties that inhibit crystal growth, crystal aggregation, dissolve Calcium Oxalate stones, and promote urinary clearance. Additionally, medicinal plants like *Kalanchoe pinnata* (Lam.) Pers., *Aegle marmelos* (L.) Corrêa, *Phyllanthus niruri* L., *Asparagus falcatus* L., and *Drymoglossum piloselloides* (L.) Presl disrupt mucoproteins, alter urinary pH, and enhance stone prevention. Their phytochemicals, including catechins, hydroxycitric acid, polyphenols, flavonoids, saponins, alkaloids, and terpenes, provide antioxidant, anti-inflammatory, diuretic effects, mitigate oxidative stress, and supersaturation. Integrating these botanicals into therapeutic regimens offers a promising, cost-effective alternative to synthetic treatments. However, standardized formulations and clinical trials are essential to confirm efficacy and safety. This review emphasizes combining traditional knowledge with scientific evidence to advance plant-based remedies for urolithiasis.

Keywords Urolithiasis, Medicinal plants, Dietary plants, Phytochemicals, Anti-urolithiatic properties

Introduction

Urolithiasis, also known as urinary calculi, urinary stones, or nephrolithiasis, is a common and recurrent health issue that affects a significant portion of the global population. These calculi can develop anywhere in the urinary tract, but they most commonly originate in the kidney [1]. Kidney stones rank third among urinary tract problems, after urinary tract infections (UTIs) and prostate disorders [2]. The condition disproportionately affects individuals aged 20–40 years, with men being three times more likely to develop urinary stones than women [3].

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The global prevalence of urolithiasis varies by region, with Asia reporting a prevalence of 1–5%, Europe 5–9%, and North America up to 13% [4]. Urinary stones are solid crystalline deposits formed from minerals and salts, classified according to their composition as calcium oxalate (CaOx), calcium phosphate ($\text{Ca}_3(\text{PO}_4)_2$), struvite, uric acid, cystine, or mixed stones [5]. Calcium-based stones, which include calcium oxalate and calcium phosphate, account for approximately 75–85% of cases and are primarily associated with elevated urinary calcium levels. Other types, such as struvite stones (2–15%), result from chronic UTIs, while uric acid stones (6–10%) are linked to high purine intake or acidic urine. Rare cystine stones (1–2%) arise from genetic disorders that cause excessive cystine excretion, whereas drug-induced stones are uncommon [6].

Most kidney stone patients experience severe pain that interferes with daily activities and may require treatment with narcotic analgesics. In addition, kidney stones can result in pyuria, hematuria, hydronephrosis, urinary obstruction, and recurrent infections. Numerous synthetic and herbal medicines have been used to facilitate stone dissolution and excretion. These treatments are generally effective for smaller stones (<6 mm in diameter) [7]. Currently, extracorporeal shock wave lithotripsy (ESWL), pharmacological therapy, and surgical removal remain the main treatment options. However, these methods are expensive, may have adverse side effects, and do not prevent stone recurrence.

Given these limitations, there is increasing interest in plant-based therapies for the prevention and management of urolithiasis. Medicinal plants possess diverse bioactive compounds such as flavonoids, saponins, alkaloids, terpenoids, phenolics, and tannins, which have been reported to exhibit anti-urolithiatic, antioxidant, anti-inflammatory, and diuretic properties. For instance, *Phyllanthus niruri* L., *Tribulus terrestris* L., *Boerhavia diffusa* L. L., and *Crataeva nurvala* Buch.-Ham. are traditionally recognized for their roles in inhibiting calcium oxalate crystallization, reducing oxidative stress, and improving renal function [8, 9].

The Ayurvedic and traditional systems of medicine strongly emphasize the use of plant-based formulations to treat urinary stones and other renal ailments [10]. Sri Lanka, endowed with rich biodiversity and a long history of traditional medicine, harbors numerous medicinal plants with potential anti-urolithiatic activity. These include species such as *Annona muricata* L. (soursop), *Kalanchoe pinnata* (Lam.) Pers., *Manilkara zapota* (L.) P.Royen, and *Garcinia cambogia* (Gaertn.) Desr. which contain bioactive compounds capable of modulating stone formation mechanisms.

Therefore, this review aims to critically examine the evidence and underlying mechanisms associated with

plant-derived compounds, particularly from Sri Lankan medicinal flora, in the management and prevention of urolithiasis. It also highlights the mechanistic pathways, therapeutic relevance, and potential of these natural remedies as effective alternatives for stone treatment and recurrence prevention.

Pathophysiology for urinary calculi formation

Urinary stone formation is a complex process involving several physicochemical stages, including supersaturation, nucleation, growth, aggregation, and retention of crystals within the kidney due to crystal–cell interactions [10]. Each of these processes is described in detail below.

Urinary supersaturation and crystallization

Calcium Oxalate (CaOx) crystallization begins with increased urinary supersaturation, forming solid crystalline particles within the urinary tract [10]. Humans naturally excrete millions of urinary crystals daily due to transient urinary supersaturation. However, the kidney's short transit time (5–10 min) prevents these crystals from growing large enough to cause blockage. Calcium oxalate (CaOx) crystals typically grow at 1–2 mm per minute and are excreted harmlessly with urine. The composition of urine largely determines crystallization [11].

Crystal nucleation

The initial step in the transformation from a liquid to a solid phase in a supersaturated solution is called nucleation. During nucleation, these stone-forming salts coalesce into clusters within the supersaturated urinary solution, which then grow in size as additional constituents attach [10].

Growth and aggregation

A nucleus's critical size initiates the start of crystal formation, which occurs under supersaturation conditions and lowers free energy when additional components are added. This process is essential for creating larger particles required for stone formation. Aggregation is the main mechanism in stone production since it has a major effect on particle size, with crystals attaching to form larger particles. Glycoproteins are macromolecules that act as a “glue” for crystals, promoting aggregation. Aggregation is considered the essential phase for crystal retention in the kidney in cases of calcium oxalate (CaOx) urolithiasis [12].

Crystal-cell interaction and stone formation

Cell damage, or pre-existing damage, facilitates the adhesion of crystals to kidney tubular epithelial cells, initiating the stone formation process [13]. Membrane vesicles and other components that support crystal attachment and nucleation are observed in injured cells [14] (Fig. 1).

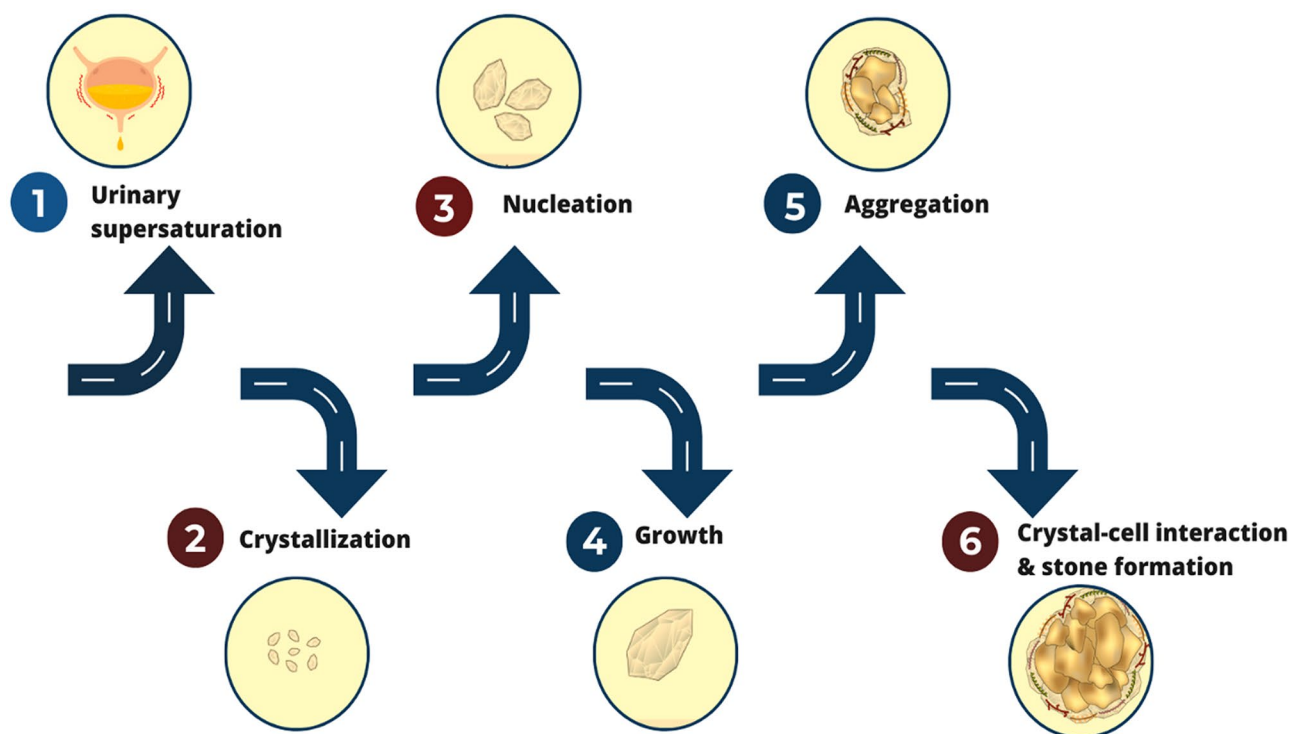


Fig. 1 Key stages in kidney stone formation (urolithiasis): a stepwise process. (This diagram outlines the sequential stages involved in kidney stone formation, starting with urinary supersaturation, followed by crystallization, nucleation, crystal growth, aggregation, and ultimately crystal-cell interaction leading to stone formation. Each stage represents a critical step in the pathophysiology of urolithiasis, providing insights into potential therapeutic targets for prevention and management)

Risk factors for urinary calculi formation

Multiple risk factors contribute to urolithiasis, including demographic characteristics (age, sex, and race), environmental factors (geographic location, climate), and lifestyle habits (diet, fluid intake, physical activity). Specific dietary practices, such as excessive consumption of salt, animal protein, and oxalate-rich foods, as well as low fluid intake, are significant contributors to urinary calculi formation. Additionally, comorbid conditions such as obesity, metabolic disorders, and genetic predispositions further increase the risk [8, 9, 15, 16] (Fig. 2).

Methodology

This narrative review was based on a comprehensive literature search conducted in PubMed, Google Scholar, ScienceDirect, MDPI, and Frontiers to identify relevant studies published between January 2000 and January 2025. Search terms included the scientific and common names of the plants under investigation, such as *Kalanchoe pinnata* (Lam.) Pers., *Annona muricata* L., *Manilkara zapota* (L.) P. Royen, and *Garcinia cambogia* (Gaertn.) Desr., together with terms related to urinary stones and kidney health, including “urolithiasis,” “urinary stones,” “kidney stones,” “crystallization,” “inhibition,” “plant extract,” “phytochemicals,” “antioxidants,” and “prevention.” Keywords were combined using

Boolean operators: (“*Kalanchoe pinnata* (Lam.) Pers.” OR “*Annona muricata* L.” OR “*Manilkara zapota* (L.) P. Royen ” OR “*Garcinia cambogia* (Gaertn.) Desr.”) AND (“urolithiasis” OR “urinary stones” OR “kidney stones”) AND (“phytochemicals” OR “antioxidants” OR “prevention” OR “crystallization”), and searches were performed within titles, abstracts, and keywords. Duplicate records were identified and removed manually.

Four reviewers independently screened titles and abstracts for relevance. Full texts were included if they (i) focused on calyx- or fruit-derived bioactive compounds such as polyphenols, flavonoids, anthocyanins, and organic acids, (ii) reported their relevance to urinary stone prevention or kidney health, and (iii) addressed outcomes related to stone formation, crystallization inhibition, or urinary parameters. Both clinical and preclinical studies were included, particularly those assessing the plants as functional foods, beverages, or therapeutic agents. Exclusion criteria were studies lacking scientific rigor, studies focused on plant parts not relevant to urinary stone prevention, studies unrelated to the review’s scope, and records without full-text access. Discrepancies in study selection were resolved through discussion until consensus was reached.

Data from eligible studies were extracted into a structured table capturing publication details, study design,

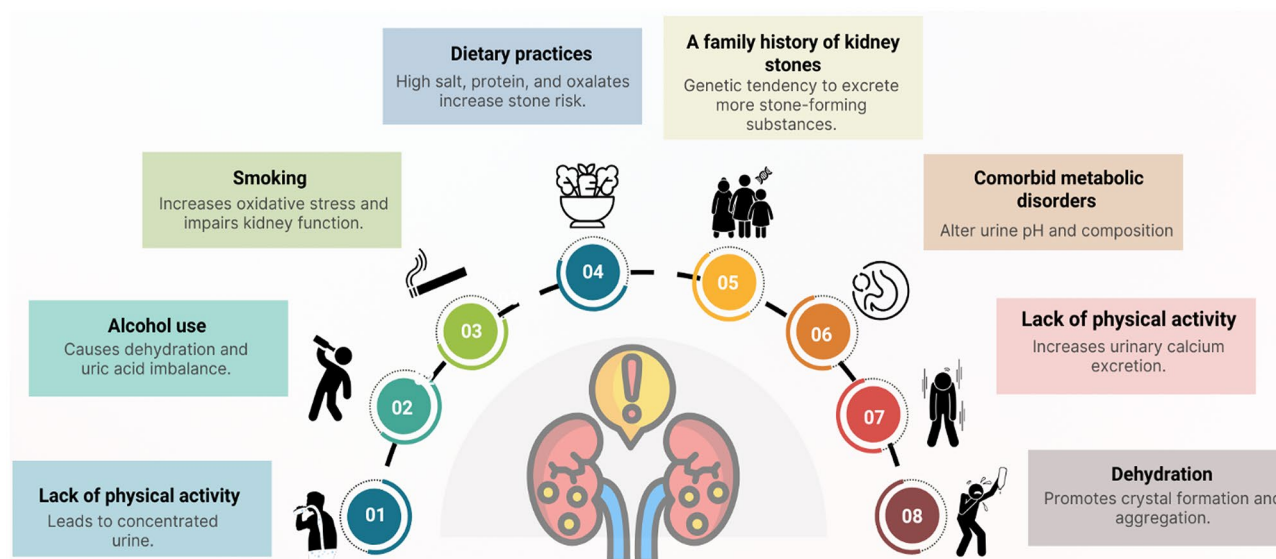


Fig. 2 Risk factors for urinary calculi formation – key contributors include genetic predisposition, dietary habits, smoking, alcohol use, lack of physical activity, obesity, low fluids intake, dehydration, excessive intake of vitamin D and C, and comorbid metabolic disorders

type of bioactive compounds investigated, intervention or dose, and reported outcomes. Evidence was synthesized thematically under three domains: (i) phytochemical composition of the plant extracts, (ii) therapeutic effects on stone formation, crystallization inhibition, and urinary parameters, and (iii) safety and toxicity. This approach enabled identification of consistent findings, controversies, and research gaps in the use of dietary plants for the prevention and management of urinary stones.

Dietary plants for prevention and management of urinary calculi

Soursop (*Annona muricata* L.)

The plant *Annona muricata* L., commonly known as soursop, which grows widely in Sri Lanka, has shown promising results in traditional medicine, particularly in managing kidney stones [17]. Its bioactive compounds, including alkaloids, flavonoids, phenolics, and acetogenins, play crucial roles in preventing urinary stone formation. These compounds exhibit antioxidant properties, reducing oxidative stress and inhibiting crystal aggregation in kidney tissues [17, 18]. Additionally, the anti-inflammatory effects of acetogenins mitigate kidney inflammation, which can exacerbate stone development [19]. The plant's diuretic activity promotes urinary mineral clearance, reducing supersaturation, and crystallization risks. Furthermore, its acidic fruit extracts enhance Calcium dissolution from stones, particularly in acidic environments. The extract's efficacy was concentration-dependent, with 100% concentrated extracts showing the highest activity. This finding highlights its role as a natural remedy with pharmacological potential against

Calcium-based kidney stones [20]. The findings suggest that *A. muricata* fruit extracts could complement existing treatments for urolithiasis, offering a natural, cost-effective alternative.

Sapodilla (*Manilkara zapota* (L.) P. Royen)

Manilkara zapota (L.) P. Royen, commonly known as chikku or sapodilla, has demonstrated potential in preventing and managing kidney stones. Its fruit contains bioactive compounds such as glycine, β -alanine, and hippuric acid, which act as crystallization inhibitors, reducing the supersaturation of calcium salts and preventing stone formation. Sapodilla juice, particularly in its acid-hydrolyzed form, exhibits significant litholytic activity, enhancing its ability to dissolve calcium-based urinary stones [21]. Acid-hydrolyzed sapodilla juice is more effective than fresh juice in dissolving kidney stones. Powdered stones showed 9.88% solubility after 72 h in acid-hydrolyzed juice, compared to only 2.64% in fresh juice, with the highest dissolution occurring in the first 48 h. Powdered stones dissolved more effectively than larger stones, indicating that juice preparation significantly impacts litholytic activity more effectively than larger stones, indicating the importance of juice preparation in enhancing litholytic activity [20, 22]. These findings suggest that sapodilla fruit, particularly its acid-hydrolyzed juice, represents a promising natural remedy for managing urolithiasis.

Garcinia cambogia (Gaertn.) Desr.

Garcinia cambogia (Gaertn.) Desr., a tropical fruit commonly used for weight loss, has shown promise in the prevention and management of kidney stones,

specifically calcium oxalate stones. Hydroxycitric acid is considered the main bioactive compound responsible for dissolving calcium oxalate crystals. Extracts of *Garcinia cambogia* (Gaertn.) Desr. at different concentrations were able to prevent the formation of calcium oxalate crystals in kidney tubules of a *Drosophila* nephrolithiasis model in a dose-dependent manner, thereby promoting their elimination. Moreover, this plant extract was found to be more effective than citric acid in preventing the formation of kidney stones and dissolving existing stones in *Drosophila* kidney tubules [21]. These results indicate that *Garcinia cambogia*, particularly in its clinically extracted form, may serve as a valuable herbal remedy for managing calcium oxalate kidney stones.

Pomegranate (*Punica granatum* L.)

Pomegranate fruit is a rich source of polyphenols, alkaloids, anthocyanins/flavonoids and antioxidants, which have great potential for free radical scavenging activity [23, 24]. All parts of this plant can be used in traditional remedies for preventive and therapeutic purposes. The anti-hypercalciuria and anti-urolithiasis effects of this plant have attracted considerable attention toward pomegranate for the prevention of urinary calculus formation. Its therapeutically beneficial phytochemicals are responsible for muscle relaxation in the urinary and biliary tracts; consequently, stones can be more easily removed from the kidney [25]. The extracts and juice of pomegranate significantly inhibited hyperoxaluria-induced oxidative kidney tubular damage due to their antioxidant and anti-lipid-peroxidation properties [26]. Pomegranate extract reduces kidney oxidative stress, thereby supporting urinary health and helping prevent urolithiasis. In a clinical trial, subjects who consumed 100 mg of pomegranate extract daily for 90 days showed a reduced incidence of kidney stones [25].

Green tea (*Camellia sinensis* (L.) Kuntze)

Green tea is the least oxidized form of tea obtained from the leaves of *Camellia sinensis* (L.) Kuntze [26]. The major catechins present in green tea are epigallocatechin (EGC), epicatechin (EC), and epigallocatechin gallate (EGCG) [27]. Studies have found that green tea exhibits anti-lithiatic properties, which could be used in the treatment of kidney stones. This property varies among different types of tea. Green tea shows the highest inhibition of stone formation, followed by oolong tea, and the least in black tea. The anti-lithiatic property of tea is mainly due to the presence of polyphenolic compounds and caffeine [27].

The high total phenolic content of green tea is major contributor to its higher efficacy against stone formation. The high total phenolic content of green tea is a major contributor to its higher efficacy against stone formation.

Green tea may prevent the formation of stones by inhibiting the aggregation of free ions in solution, thereby preventing them from forming microscopic particles due to its capping and reducing properties [28]. Green tea significantly reduces Oxalate crystal formation and inhibits the soluble protein components responsible for stone formation in rat kidneys treated with tea extract [28]. A study reported that green tea EGCG inhibited Calcium Oxalate deposition in rats by enhancing superoxide dismutase (SOD) activity [29]. Intercellular radical species generated from lipid peroxidation of membranes contribute to Calcium Oxalate crystal formation in hyperoxaluria. Green tea has been found to reduce such kidney injury caused by oxidative stress, thus inhibiting nucleation in rat kidneys. Studies conducted in Normal Rat Kidney (NRK) cell lines reported that green tea catechins play an important role in neutralizing free radicals and reducing Oxalate formation, highlighting their potential as a therapeutic agent against urolithiasis [29, 30] (Table 1).

Medicinal plants as dietary supplements for prevention and management of urinary calculi

Medicinal plants have long been integral to traditional medicine for preventing and managing kidney stones, or nephrolithiasis. Recent scientific investigations have provided empirical support for their efficacy, highlighting various mechanisms through which these botanicals exert anti-urolithiatic effects.

***Kalanchoe pinnata* (Lam.) Pers. (Akkapana)**

The aqueous extract of *Kalanchoe pinnata* (Lam.) Pers. has been administered orally in some countries for the treatment of urinary calculi. It enhances kidney function, as evidenced by increased estimated GFR (Glomerular Filtration Rate) and decreased blood urea, along with reduced urinary Oxalate levels in rats. The recommended dose is to chew three leaves twice daily [34]. The aqueous paste made from *K. pinnata* and *Eclipta prostrata* (L.) L. in equal amounts possesses excellent anti-renal calculi activity when administered orally. *K. pinnata* extract demonstrated pronounced effectiveness in dissolving Calcium Oxalate calculi. After five washes, the extract could dissolve approximately 30% of Calcium Oxalate crystals and reduce actual kidney stone weight by 18%, compared to only 17% dissolution with deionized water [33]. *The active components—organic acids, saponins, and proteins—contribute to this effect by inhibiting crystal growth, aggregation, and retention. Organic acids chelate Calcium ions, saponins disrupt mucoproteins to inhibit crystallization, and proteins act as surface barriers that prevent aggregation. Additionally, the extract promotes the formation of less harmful Calcium Oxalate crystals, highlighting its potential as a therapeutic agent* [35].

Table 1 Key dietary plants and their anti-urolithiatic properties – summary of plant parts, study types, extracts, dose, phytochemicals, and mechanisms of action

Plant	Part of Plant	Study Type	Extract Preparation / Solvent	Dose / Concentration	Major Phytochemicals	Key Findings	Reference
Soursop (<i>Annona muricata</i> L.)	Fruit, Leaves	In-vitro: CaOx dissolution In-vivo: Rat model, crystal inhibition	Methanol / Aqueous extract	In vitro: 50–200 µg/mL In vivo: 200–400 mg/kg body weight	Alkaloids, flavonoids, phenolics, acetogenins	• Antioxidant properties reducing oxidative stress and inhibition of crystal aggregation. • Diuretic activity promoting mineral clearance. • Acidic extracts dissolving calcium stones.	[17–20]
Sapodilla (<i>Manilkara zapota</i> (L.) P. Royen)	Fruit	In-vitro: Acid-hydrolyzed juice	Acid-hydrolyzed juice	100–250 µg/mL	Glycine, β-alanine, hippuric acid	• Bioactive compounds inhibit crystallization. • Acid-hydrolyzed juice effectively dissolves kidney stones.	[22]
<i>Garcinia cambogia</i> (Gaertn.) Desr.	Fruit	In-vivo: Rat model, Drosophila model In-vitro: Crystal inhibition assay	Hydroalcoholic extract	In vivo: 300 mg/kg body weight; In vitro: 50–150 µg/mL	Hydroxycitric acid, polyphenols, flavonoids	• Hydroxycitric acid prevents crystal formation, promotes elimination, and is more effective than citric acid.	[21]
Pomegranate (<i>Punica granatum</i> L.)	Fruit, Whole Plant	In-vitro: CaOx inhibition assays Clinical: Human trials in stone formers	Methanol / Aqueous extracts	In vitro: 50–200 µg/mL; Clinical: 250 mL juice/day	Polyphenols, alkaloids, anthocyanins/flavonoids	• Anti-oxidant-rich extracts reduce oxidative stress. • Aid muscle relaxation and lower kidney stone incidence.	[23–26]
Green tea (<i>Camellia sinensis</i> (L.) Kuntze)	Leaves	In-vitro: Crystal aggregation assays In-vivo: Rat ethylene glycol model	Aqueous extract / Catechin-rich infusion	In vitro: 50–200 µg/mL; In vivo: 100–300 mg/kg body weight	Catechins (EGC, EC, ECG), polyphenols, caffeine	• Catechins and polyphenols prevent oxalate crystal formation. • Reduce oxidative stress. • Neutralize free radicals.	[27–33]

***Aegle marmelos* (L.) Corrêa**

Aegle marmelos (L.) Corrêa, commonly referred to as “Beli” in Sri Lanka, is a plant of immense potential for the prevention and management of urinary calculi disorders due to its anti-urolithiatic properties. Ethanol and hexane extracts from flowers of *Aegle marmelos* (L.) Corrêa were studied in vitro for inhibiting nucleation, growth, and aggregation of calcium oxalate (CaOx) crystals in a dose-dependent manner. Hexane extract at 1000 µg/mL displayed the highest percentage inhibition rates on nucleation and aggregation, 83.56% and 50.13%, respectively, much higher than that of the standard drug Cystone. These effects are attributed to phytochemicals such as saponins, anthracene glycosides, and reducing sugars, which interfere with crystal formation and growth. Saponins, for example, disrupt mucoproteins that facilitate crystal aggregation, while glycosides and sugars reduce supersaturation and alter the ionic composition in synthetic urine models. Additionally, microscopic analysis revealed a dose-dependent reduction in crystal formation, emphasizing the therapeutic potential of *A. marmelos* in urolithiasis prevention [36].

***Drymoglossum piloselloides* (L.) Presl**

Drymoglossum piloselloides (L.) Presl, commonly known as “Kasi pethi” in Sri Lanka, exhibits significant potential in preventing and managing kidney stones [35]. Results obtained from in vitro studies showed that leaf extracts from *D. piloselloides* effectively inhibited calcium oxalate (CaOx) crystal nucleation, growth, and aggregation. Among the studied extracts, ethanol extract exhibited the highest activity, with nucleation and aggregation inhibition rates of 73.43% and 58.36%, respectively, at a dose of 1000 µg/mL. These results were comparable to those elicited by the standard anti-urolithiatic drug Cystone, underlining the therapeutic potential of the plant [36].

Phytochemical screening of the *D. piloselloides* leaf extracts showed that they contain tannins, flavonoids, and phenolic acids, which may inhibit CaOx crystallization by influencing kidney tissue supersaturation and/or reducing associated oxidative stress. The extracts also disrupt mucoproteins that facilitate crystal aggregation, thereby reducing stone formation. Microscopic analysis confirmed a dose-dependent decrease in crystal size and number, further supporting its anti-urolithiatic efficacy [36].

***Phyllanthus niruri* L.**

Phyllanthus niruri L., also known as “Pitawakka” in Sri Lanka, has been traditionally used and extensively investigated for its anti-urolithiatic activities. It has been reported that *P. niruri* significantly inhibits CaOx crystal growth, nucleation, and aggregation, which are critical steps during the formation of kidney calculi. A 42-day

study using an animal model of urolithiasis demonstrated a considerable reduction in both the size and number of calculi after chronic administration of an aqueous extract of *P. niruri* compared to untreated groups. Interestingly, some treated animals completely eliminated the introduced CaOx crystals, highlighting the plant's potential to dissolve stones [37]. The protective effects of *P. niruri* are attributed to its ability to interfere with crystal adhesion to kidney epithelial cells and modulate glycosaminoglycan (GAG) incorporation into calculi. This activity occurs independently of changes in urinary citrate or magnesium levels, suggesting that *P. niruri* primarily acts on the crystalline matrix itself. Additionally, the plant has been shown to exert antispasmodic and analgesic effects, facilitating the elimination of smaller calculi and reducing associated pain [38]. Clinical studies have demonstrated that *P. niruri* administration leads to a significant reduction in urinary Calcium levels among hypercalciuric patients, thereby decreasing the risk of Calcium Oxalate stone formation. Additionally, regular intake of *P. niruri* extract post-extracorporeal shock wave lithotripsy (ESWL) has been associated with increased stone-free rates, suggesting its role in preventing stone recurrence [39].

***Asparagus falcatus* L.**

Asparagus falcatus L. is a widely used medicinal plant in the traditional medicine systems of Sri Lanka, which has shown promising anti-urolithiatic properties for the prevention and management of urinary calculi. The methanolic root extract of *A. falcatus* has demonstrated efficacy in inhibiting calcium oxalate crystal nucleation and aggregation, which are critical processes in kidney stone formation. Its traditional use as a potent anti-urolithiatic agent supports the development of *A. falcatus* as an alternative treatment for urinary calculi [40] (Table 2).

Active phytochemicals and their mechanisms in inhibition of urinary calculi

Phytochemicals are a class of bioactive plant compounds that play a critical role in preventing and managing urinary calculi due to their multifunctional nature. These substances act at various stages of urinary calculi formation, such as nucleation, growth, aggregation, and dissolution, making them effective natural agents against urolithiasis, as illustrated in Fig. 3.

Polyphenols

Polyphenols, widely found in green tea (*Camellia sinensis* (L.) Kuntze), act as powerful antioxidants that help diminish oxidative stress, a major contributor to kidney stone formation. Reactive oxygen species (ROS) promote crystal formation by damaging kidney cells and increasing calcium oxalate aggregation. Polyphenols, such as

catechins, scavenge ROS, stabilize kidney tissues, and inhibit the crystallization of calcium oxalate [37]. Catechins from green tea have been particularly effective in reducing crystal growth and adhesion by forming stable complexes with calcium ions, thereby preventing supersaturation and nucleation [39].

Flavonoids

Flavonoids, abundantly found in citrus fruits, parsley, and berries, possess strong antioxidant, anti-inflammatory, and diuretic properties. Quercetin, a flavonoid commonly found in onions and apples, reduces oxidative stress and inhibits crystal aggregation [42]. Flavonoids also prevent crystal retention and facilitate crystal excretion by minimizing inflammation and oxidative damage in the renal epithelium. Additionally, they modulate the expression of adhesion-related proteins, further reducing the likelihood of stone formation [40].

Saponins

Saponins are natural surfactants that lower the surface tension of urine, thereby preventing crystal aggregation. Moreover, they complex oxalate ions, reducing their availability for crystallization. Their diuretic properties enhance urine output, facilitating the flushing of small crystals and decreasing supersaturation of stone-forming minerals [8].

Alkaloids

Alkaloids, present in *Phyllanthus niruri* L. and tea leaves, exhibit potent anti-inflammatory and analgesic effects while exerting crystal-inhibitory actions through the regulation of calcium and oxalate metabolic pathways. These mechanisms help restrict the nucleation and growth of crystals. Studies involving *Phyllanthus niruri* L. have also demonstrated a significant reduction in calcium oxalate deposition and enhanced stone dissolution by modulating urinary pH and increasing citrate excretion [8].

Terpenes

Terpenes possess significant anti-inflammatory and diuretic properties. They enhance urine production, which aids in flushing out small crystals and decreases the urinary supersaturation of salts. Terpenes inhibit calcium oxalate (CaOx) aggregation by adhering to crystal surfaces, thereby preventing their growth and aggregation [42].

Phytates (Inositol Hexakisphosphate)

Phytates play a protective role in urolithiasis by reducing urinary calcium excretion and preventing calcium oxalate precipitation. By binding calcium in the gut, phytates reduce its availability for stone formation and inhibit crystallization. Another mechanism involves modulating

Table 2 Key medicinal plants and their anti-urolithiatic properties – summary of plant parts, study types, extracts, dose, phytochemicals, and mechanisms of action

Plant	Part of Plant	Study Type	Extract Preparation / Solvent	Dose / Concentration	Major Phytochemicals	Anti-Urolithiatic Property	Reference
<i>Kalanchoe pinnata</i> (Lam.) Pers. (Akkapana)	Leaves	In vivo (rat) and in vitro	Aqueous / Methanol extract	In vivo: 200–400 mg/kg; In vitro: 50–150 µg/mL	Organic acids, saponins, proteins	• Dissolves Calcium Oxalate monohydrate (COM) crystals, promotes formation of less harmful COD crystals. • Contains organic acids, saponins, and proteins that inhibit crystal aggregation and retention.	[34–36]
<i>Aegle marmelos</i> (L.) Corrêa (Beli)	Flowers	In vitro	Ethanol / Hexane extract	50–200 µg/mL	Saponins, anthracene glycosides, sugars	• Ethanol and hexane extracts inhibit CaOx crystal nucleation, growth, and aggregation. • Saponins and glycosides disrupt mucoproteins, reducing supersaturation and promoting ionic balance in urine.	[41]
<i>Drymoglossum piloselloides</i> (L.) Presl (Kasi Pethi)	Leaves	In vitro	Ethanol extract	50–200 µg/mL	Tannins, flavonoids, phenolic acids	• Ethanol extracts inhibit CaOx crystal nucleation and aggregation. • Rich in tannins, flavonoids, and phenolic acids, which reduce oxidative stress and prevent crystal growth. • Shows dose-dependent reduction in crystal size and number.	[38, 41]
<i>Phyllanthus niruri</i> L. (Pitawakka)	Whole plant	In vivo (rat) and clinical	Aqueous / Methanol extract	In vivo: 300 mg/kg; Clinical: 250 mL juice/day	Lignans, flavonoids, alkaloids	• Reduces crystal adhesion, growth, and recurrence. • Modulates glycosaminoglycan incorporation and exhibits anti-spasmodic properties. • Enhances Calcium excretion post-lithotripsy, leading to higher stone-free rates and decreased recurrence risk.	[37, 39, 42]
<i>Asparagus falcatus</i> L.	Roots	In vitro	Methanolic extract	50–150 µg/mL	Saponins, flavonoids	• Methanolic extract inhibits CaOx crystal nucleation and aggregation. Promotes stone dissolution. • Contains anti-inflammatory phytochemicals like curcumin, reducing kidney inflammation and oxidative stress. • Demonstrates efficacy similar to marketed formulations.	[40]

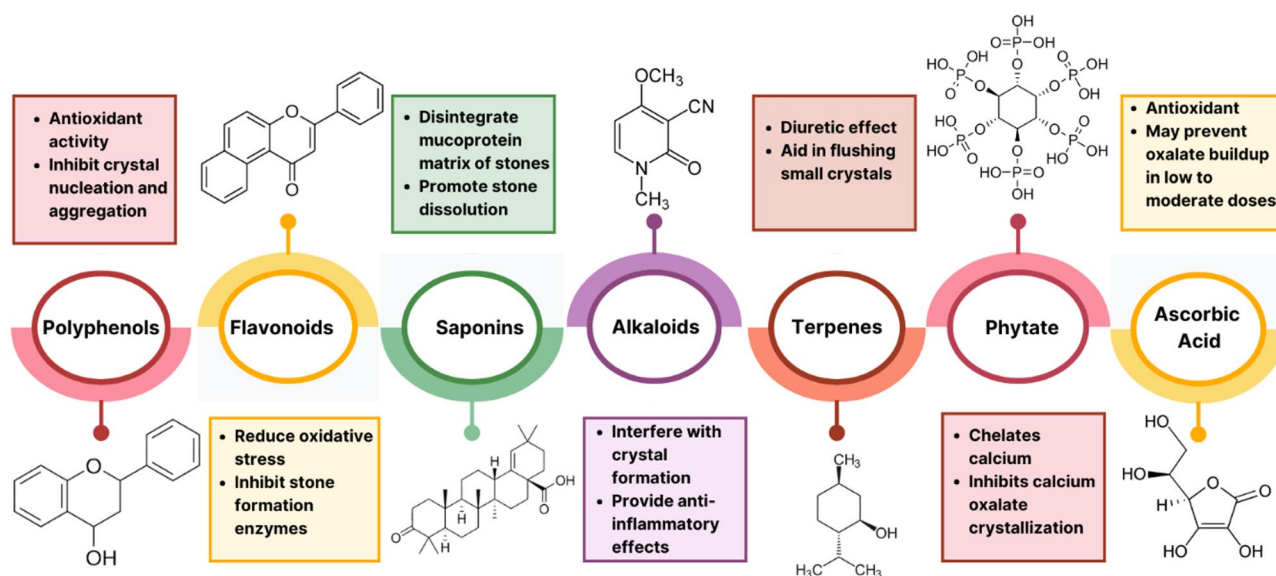


Fig. 3 Phytochemical classes and representative structures with potential roles in the prevention and management of urolithiasis (This diagram highlights key bioactive compounds, including polyphenols, flavonoids, saponins, alkaloids, terpenes, phytate, and ascorbic acid, along with their molecular structures, emphasizing their therapeutic, and preventive applications in kidney stone management)

urinary pH, creating an unfavorable environment for crystal growth [43].

Ascorbic acid (Vitamin C)

Vitamin C functions as a potent antioxidant, helping to reduce oxidative stress in kidney tissues. However, in excessive amounts, it can increase oxalate excretion, potentially raising the risk of stone formation. Therefore, moderate intake of this vitamin is essential to balance its antioxidant benefits with its potential lithogenic effects [39].

Phytochemicals present a multifaceted approach to the prevention and management of urinary calculi, acting through their antioxidant activity, inhibition of crystallization, diuretic effects, anti-inflammatory properties, ion chelation, and modulation of urinary pH. Collectively, these actions target multiple stages of stone pathogenesis, offering a promising natural strategy for urolithiasis management.

Mechanisms and actions of plant bioactive compounds in the prevention and management of urolithiasis

Recent studies have elucidated the multifaceted mechanisms through which plant-derived bioactive compounds contribute to the prevention and management of urinary calculi (kidney stones). These mechanisms encompass antioxidant, anti-inflammatory, diuretic, and crystallization-inhibitory effects, among others. Below is a detailed exploration of these mechanisms, supported by recent scientific evidence.

Antioxidant activity

Oxidative stress plays a pivotal role in the formation and progression of kidney stones. Reactive oxygen species (ROS) can damage renal cells and promote crystallization of stone-forming minerals. Plant polyphenols, such as those found in green tea (*Camellia sinensis* (L.) Kuntze), pomegranate (*P. granatum*), and soursop (*A. muricata*), exhibit potent antioxidant properties. These compounds scavenge ROS, thereby protecting renal tissues from oxidative damage and inhibiting the nucleation and growth of calcium oxalate crystals [44].

Anti-inflammatory effects

Chronic inflammation within the renal system can facilitate the aggregation of crystallized minerals, leading to stone formation. Flavonoids and alkaloids present in plants like *Aegle marmelos* (L.) Corrêa and *Phyllanthus niruri* L. possess anti-inflammatory properties. These compounds modulate inflammatory pathways, such as the downregulation of pro-inflammatory cytokines and inhibition of cyclooxygenase enzymes, thereby reducing inflammation and preventing crystal aggregation [45].

Diuretic action

Increased urine output aids in the dilution of stone-forming substances and promotes their excretion. Plants like *Kalanchoe pinnata* (Lam.) Pers. and *Asparagus falcatus* L. exhibit diuretic effects by enhancing renal blood flow and glomerular filtration rate. This increased urine production helps flush out small crystals and reduces the supersaturation of urine, thereby preventing stone formation [45].

Inhibition of crystallization and aggregation

The formation of kidney stones involves the nucleation, growth, and aggregation of crystals. Phytochemicals such as saponins, flavonoids, and alkaloids interfere with these processes. For instance, saponins reduce the surface tension of urine, preventing crystal aggregation. Flavonoids alter the ionic composition of urine, reducing supersaturation, while alkaloids chelate calcium ions, inhibiting crystal growth [45].

Litholytic (Stone-Dissolving) properties

Certain plant extracts possess the ability to dissolve existing kidney stones. For example, acid-hydrolyzed sapodilla (*Manilkara zapota* (L.) P. Royen) juice has demonstrated litholytic activity by breaking down calcium-based stones into smaller, more easily excretable particles. Similarly, extracts from soursop fruit have been shown to enhance calcium dissolution from stones, particularly in acidic environments [45].

Modulation of urinary pH

The pH of urine significantly influences the solubility of stone-forming minerals. Some plant extracts can modulate urinary pH, creating an environment less conducive to crystal formation. For instance, pomegranate extracts have been shown to alkalinize urine, thereby reducing the risk of calcium oxalate and uric acid stone formation [45].

Chelation of stone-forming minerals

Phytochemicals such as phytates and certain organic acids can chelate calcium and oxalate ions, reducing their availability for crystallization. This chelation prevents the formation of insoluble salts and inhibits the initial stages of stone formation [45].

Mechanisms of renal epithelial injury and therapeutic targets in urolithiasis

Crystal adhesion to renal tubular epithelial cells

The adhesion of CaOx crystals to the renal tubular epithelial cells is a critical step in kidney stone formation. This interaction initiates a cascade of events leading to epithelial injury, inflammation, and fibrosis. Crystals induce oxidative stress by generating reactive oxygen species (ROS), which damage cellular components and activate inflammatory pathways. This process is associated with the upregulation of kidney injury markers such as KIM-1 and α -SMA, indicating tubular damage and myofibroblast transformation [46].

Modulation of urinary proteins

Urinary proteins play a significant role in regulating crystal formation and adhesion. In stone formers, alterations in the composition and concentration of these proteins can promote crystal aggregation and adhesion to the

renal epithelium. For instance, decreased levels of inhibitors like Tamm-Horsfall protein and increased levels of promoters such as osteopontin have been observed in individuals prone to stone formation [47].

Recent studies have highlighted the importance of targeting renal epithelial injury and urinary protein modulation in the prevention and management of urolithiasis. Therapeutic strategies aim to reduce crystal adhesion, restore the balance of urinary proteins, and mitigate oxidative stress and inflammation. For example, natural compounds with antioxidant and anti-inflammatory properties have shown promise in protecting renal tubular cells from crystal-induced injury and in modulating the expression of urinary proteins to favor stone prevention [48].

Adverse effects, interactions, and toxicities of medicinal plants

Herbal and dietary supplements, despite their natural origin, are not devoid of pharmacological risks. Certain bioactive constituents may induce organ-specific toxicities, particularly hepatotoxicity and nephrotoxicity, when consumed in excessive or unregulated doses. Additionally, these preparations can interact with conventional pharmaceuticals through pharmacokinetic mechanisms altering drug absorption, metabolism, or excretion via pharmacodynamic interactions that modify therapeutic efficacy or enhance toxicity. Furthermore, unpredictable idiosyncratic reactions have been documented with several botanical agents. Consequently, both healthcare professionals and patients should exercise the same level of vigilance applied to conventional pharmacotherapies, systematically recording herbal use, monitoring biochemical and clinical parameters, and avoiding unsupervised or high-dose supplementation [49].

Hepatotoxicity

Although most medicinal plants are perceived as safe, some can cause significant liver toxicity, particularly when consumed in concentrated extract form. *Garcinia cambogia* (Gaertn.) Desr., widely used for weight loss, has been linked to acute liver injury in several case reports and clinical reviews, often associated with high doses of hydroxycitric acid supplements. Similarly, green tea extracts, rich in epigallocatechin gallate (EGCG), may cause idiosyncratic hepatotoxicity when used in concentrated supplement form, though moderate tea consumption is considered safe. Therefore, it is essential to monitor liver function in individuals consuming these extracts for prolonged periods, especially when used concurrently with other medications affecting liver metabolism [50].

Nephrotoxicity

Certain herbal remedies may adversely affect renal function, particularly when used in excess or combined with nephrotoxic drugs. Herbal nephrotoxicity may result from oxidative damage, precipitation of plant metabolites, or contamination with heavy metals. Long-term or unregulated use of some herbal preparations has been linked to acute interstitial nephritis and renal impairment in sensitive individuals. Patients with pre-existing kidney disease should be advised to use herbal remedies cautiously and under medical supervision [51].

Neurotoxicity

Annona muricata L. (soursop), though beneficial for kidney stone prevention, contains acetogenins such as annonacin, which may cause neurotoxic effects after long-term or high consumption. Studies suggest that excessive intake of soursop products could contribute to atypical Parkinsonism due to the inhibition of mitochondrial complex I in neuronal cells. Hence, regular or high-dose use of *Annona muricata* L. extracts should be approached cautiously, with preference given to moderate dietary use rather than concentrated supplementation [52].

Cardiac toxicity

Kalanchoe pinnata (Lam.) Pers. and related species contain bufadienolide-type cardiac glycosides, compounds that can cause cardiotoxicity if consumed in large quantities. These glycosides may interfere with cardiac conduction and potentially lead to arrhythmias. While the small quantities present in traditional preparations are generally safe, standardized dosing and controlled extraction are crucial to minimize cardiac risk [53].

Herb–drug interactions

Several plant extracts have been found to interact with conventional medications, altering their absorption, metabolism, or elimination. *Punica granatum* L. (pomegranate) juice and extracts, for example, can inhibit cytochrome P450 enzymes (CYP3A4 and CYP2C9), which may affect the metabolism of drugs such as warfarin, statins, and certain antihypertensives. Similarly, green tea catechins and *Phyllanthus niruri* L. extracts can influence the pharmacokinetics of various drugs by modulating drug transporters and metabolic enzymes. Therefore, individuals taking prescription medications should consult healthcare professionals before using these herbal products [49, 54].

General safety considerations

Although dietary levels of these plants are generally safe, excessive or unregulated consumption of concentrated extracts may lead to adverse reactions. Most available

safety data are derived from in vitro or animal studies, with limited clinical evidence in humans. Hence, standardization of extracts, dose optimization, and toxicological evaluation are essential to ensure safety. Monitoring liver and kidney function during prolonged use and avoiding combinations with hepatotoxic or nephrotoxic drugs is strongly recommended [55].

Discussion

Plant-derived bioactive compounds have emerged as promising agents in the prevention and management of urolithiasis. Recent studies have shown that these compounds inhibit calcium oxalate crystallization, a critical early step in kidney stone formation. Phytochemicals interfere with crystal nucleation, growth, and aggregation, reducing the likelihood of stone formation [56].

In addition to crystallization inhibition, many plant compounds exert antioxidant and anti-inflammatory effects. Polyphenols, flavonoids, and saponins enhance cellular antioxidant defenses through the Nrf2 pathway while suppressing inflammatory responses via NF- κ B inhibition. This dual action reduces oxidative stress and inflammation in renal tissues, protecting against renal injury [46].

Bioactive compounds also modulate urinary proteins, which play a key role in crystal retention and adhesion. By restoring inhibitors such as Tamm-Horsfall protein and reducing promoters like osteopontin, these compounds prevent crystal aggregation and attachment to the renal epithelium, further reducing stone formation risk [57].

Finally, plant-derived compounds protect renal tubular cells from crystal-induced injury. They scavenge reactive oxygen species and modulate signaling pathways involved in apoptosis and fibrosis, helping maintain epithelial integrity and renal function. Together, these findings highlight the multifaceted protective roles of plant-derived bioactive compounds in urolithiasis. Therapeutic strategies that harness these mechanisms could provide a holistic and effective approach to kidney stone prevention and renal health [58].

Challenges and future perspectives

Dietary plants and their bioactive components demonstrate significant promise in the prevention and management of urolithiasis. The major challenge, however, remains the translation of these findings into clinical practice. A primary limitation for most of these plants is the lack of well-designed human clinical trials to establish their efficacy and safety. Most available evidence is therefore derived from in vitro and animal studies. While these studies are invaluable, their results cannot be directly extrapolated to human metabolism and physiology. It is thus necessary to bridge this gap by confirming the

pharmacological effects observed in preclinical models and validating their applicability in human populations.

Standardization of plant extracts and their bioactive compounds is crucial due to variability in sources, cultivation methods, and extraction techniques. Such variability leads to inconsistencies in active ingredient composition, complicating dose optimization and reproducibility. Developing standardized extraction protocols and identifying key biomarkers are essential to ensure consistency and efficacy. Further investigations into the molecular mechanisms underlying anti-urolithiatic effects are also needed, with advances in molecular biology and metabolomics potentially aiding in the identification of new therapeutic targets.

Future research should emphasize the long-term safety and potential side effects of plant-based remedies for urolithiasis. Evaluating their interactions with conventional medications and effects on pre-existing health conditions is essential. Additionally, understanding the bioavailability and metabolic pathways of phytochemicals is critical for assessing therapeutic effectiveness. Investigations into optimal dosage, frequency, and formulation will enhance their clinical utility. Interdisciplinary approaches, integrating pharmacology, nutrition, and clinical sciences, alongside modern technologies such as nanotechnology and targeted drug delivery systems, may further improve the efficacy of plant-based treatments for kidney stone prevention and management.

Statements and declarations

The author(s) of this article do not have any conflicts of interest related to the research, authorship, or publication of the work.

Conclusion

Urinary calculi pose a significant health burden globally. While conventional treatments provide management options, they often have limitations. This review highlights the potential of medicinal plants and their bioactive compounds in preventing and managing urolithiasis. Numerous plants, including *Annona muricata* L., *Manilkara zapota* (L.) P. Royen, *Garcinia cambogia* (Gaertn.) Desr., *Punica granatum* L., *Camellia sinensis* (L.) Kuntze, *Kalanchoe pinnata* (Lam.) Pers., *Aegle marmelos* (L.) Corrêa, *Drymoglossum piloselloides* (L.) Presl, *Phyllanthus niruri* L., and *Asparagus falcatus* L., exhibit promising anti-urolithiatic properties through various mechanisms. These include inhibiting crystal formation, promoting dissolution, and exerting antioxidant and anti-inflammatory effects. However, further research is crucial to establish clinical efficacy, optimize dosages, and ensure safety. Standardization of plant extracts and rigorous clinical trials are essential to translate the

potential of these natural remedies into effective and safe therapeutic options for urolithiasis management.

Author contributions

A.G.K. and G.M. wrote the main manuscript text. A.G.K., G.M., and A.G.K.C. contributed to the conceptualization. A.G.K. prepared the figures and tables. G.M., A.G.K.C., A., K.M.S., K.P., H.T.L., and S.G.A. contributed to review and editing. H.T.L. and A.G.K. managed the references. G.M. provided supervision. All authors reviewed the manuscript.

Funding

The authors received no financial support for the research, authorship, and/or publication of this review article.

Data availability

No datasets were generated or analysed during the current study.

Declarations

Competing interests

The authors declare no competing interests.

Received: 8 June 2025 / Accepted: 18 February 2026

Published online: 06 March 2026

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