International Urology and Nephrology
https://doi.org/10.1007/s11255-024-04148-9

UROLOGY – REVIEW

Plant-based therapies for urolithiasis: a systematic review of clinical and preclinical studies

Essmat A. H. Allam[1] · **Mahmoud S. Sabra**[2]

Received: 27 May 2024 / Accepted: 3 July 2024

Abstract

Purpose Urolithiasis, the formation of kidney stones, is a common and severe condition. Despite advances in understanding its pathophysiology, affordable treatment options are needed worldwide. Hence, the interest is in herbal medicines as alternative or supplementary therapy for urinary stone disease. This review explores the use of plant extracts and phytochemicals in preventing and treating urolithiasis.

Methods Following PRISMA standards, we systematically reviewed the literature on PubMed/Medline, focusing on herbal items evaluated in in vivo models, in vitro studies, and clinical trials related to nephrolithiasis/urolithiasis. We searched English language publications from January 2021 to December 2023. Studies assessing plant extracts and phytochemicals' therapeutic potential in urolithiasis were included. Data extracted included study design, stone type, plant type, part of plant used, solvent type, main findings, and study references.

Results A total of 64 studies were included. Most studies used ethylene glycol to induce hyperoxaluria and nephrolithiasis in rat models. Various extraction methods were used to extract bioactive compounds from different plant parts. Several plants and phytochemicals, including *Alhagi maurorum*, *Aerva lanata*, *Dolichos biflorus*, *Cucumis melo*, and quercetin, demonstrated potential effectiveness in reducing stone formation, size, and number.

Conclusions Natural substances offer an alternative or supplementary approach to current treatments, potentially reducing pain and improving the quality of life for urolithiasis patients. However, further research is needed to clarify their mechanisms of action and optimize their therapeutic use. The potential of plant-based therapies in treating urolithiasis is promising, and ongoing research is expected to lead to treatment advancements benefiting patients globally.

Keywords Nephrolithiasis · Kidney stones · Calcium oxalate · Phytochemicals · Urinary calculi

Introduction

Kidney stones or urolithiasis results from the buildup of solid mineral and salt deposits in the urinary system or kidneys. These deposits can induce severe pain and discomfort; potential problems, such as infection or urinary tract blockage, could arise if they are not addressed. The incidence and the prevalence of urolithiasis exhibit significant variation across different populations. According to some estimations, this condition might impact as much as 10–15% of the world's population [1].

The burden of urolithiasis is substantial in terms of its impact on individual patients and its broader economic and healthcare costs. Kidney stones can cause severe pain and discomfort, often necessitating hospitalization or surgical intervention for removal. Beyond the direct costs of treatment, urolithiasis can also result in lost productivity and diminished quality of life for affected individuals. Moreover, emerging evidence links nephrolithiasis to an increased risk of chronic kidney disease (CKD) [2].

The etiology of urolithiasis is sophisticated and remains incompletely understood. The production of kidney stones is believed to be motivated by a mixture of factors, such as nutrition, genetics, underlying medical conditions, and specific drugs. Stones frequently result when urine gets concentrated, facilitating the crystallization and adhesion of

✉ Essmat A. H. Allam
essmatallam@pharm.aun.edu.eg

[1] Department of Pharmacology and Toxicology, Faculty of Pharmacy, Assiut University, Assiut 71526, Egypt

[2] Pharmacology Department, Faculty of Veterinary Medicine, Assiut University, Egypt 71526, Egypt

Published online: 23 July 2024

minerals. After their formation, these crystals can undergo further growth, eventually forming more giant stones that can provoke pain and other symptoms [3].

Also, present therapies for urolithiasis incorporate both medicinal and surgical methods. Petite stones may pass naturally with pain medication and increased fluid consumption in certain circumstances. Nonetheless, larger stones or those causing troubles may demand more intrusive therapies such as shock wave lithotripsy or ureteroscopy for removal. While these therapies can effectively remove existing stones, recurrence is expected, and they do not state the fundamental causes of stone formation.

There are drawbacks to current treatments for urolithiasis. For instance, surgical interventions carry risks such as infection or bleeding and may not be appropriate for all patients. Medical treatments such as thiazide diuretics or potassium citrate can help counteract stone recurrence in some cases but may not be helpful for all types of stones. Furthermore, these treatments need continuing checking and may have side effects [4].

Given these limitations, there is considerable interest in using plant extracts and phytochemicals to prevent and treat urolithiasis. Many herbs have been traditionally utilized for their diuretic or antispasmodic qualities, which may help facilitate the transit of kidney stones. Additionally, several plant chemicals have been proven to decrease the crystallization or aggregation of minerals in the urine, potentially reducing the likelihood of stone formation [5]. Urolithiasis has traditionally been treated using a variety of herbal remedies, including *Crataeva magna*, *Aerva javanica*, *Ipomoea eriocarpa*, *Peperomia tetraphylla*, *Punica granatum*, *Terminalia bellirica*, *Hibiscus rosa-sinensis*, *Moringa oleifera*, and *Costus spiralis* [6]. To dissolve kidney stones and stop them from coming back, people have turned to anti-urolithiatic herbs in various forms, such as decoction, infusion, or juice. There are fewer side effects and lower costs when using medicinal plants, but their efficacy is lower, and the period of therapy is longer. Additional scientific investigations are required to investigate safe and natural anti-urolithiatic substances based on the ethnopharmacological data that is now accessible [7]. Phytochemicals contain complex molecular structures that work across various metabolic pathways to deliver desired medicinal effects. Some of these secondary metabolites are bioactive, with high selectivity for cellular targets. In contrast, some metabolites have several cellular targets that may cooperate to produce a specific biological activity. Also, phytochemicals can create biological activity through synergistic processes [8].

Current evidence-based guidelines for managing urolithiasis, such as those from the European Association of Urology (EAU), recommend increasing fluid intake, maintaining a balanced diet, and engaging in regular physical activity to prevent stone formation [9]. In addition, weight management is emphasized as a crucial factor in reducing the risk of stone recurrence [10]. While these lifestyle modifications are effective, they may only be sufficient for some patients, particularly those with recurrent stones or underlying metabolic disorders.

Herbal treatments can provide specific bioactive compounds that inhibit stone formation, reduce oxidative stress, and improve renal function. By integrating herbal treatments with conventional recommendations, we can offer a more comprehensive approach to managing urolithiasis. This combined strategy may enhance patient outcomes, particularly for those who do not respond adequately to lifestyle modifications alone.

In conclusion, urolithiasis is a frequent and significant disorder that can cause considerable pain and discomfort for affected individuals. While current therapies can help relieve existing stones, there are limits to these techniques, and recurrence is likely. This systematic review outlines the utilization of plant extracts and phytochemicals as a potential field of research for the prevention and treatment of urolithiasis to give specific references for further study.

Methodology

Search strategy

A comprehensive literature search was conducted using five databases: PubMed, Web of Science, Cochrane Database of Systematic Reviews, Medline, and Scopus. The search was limited to articles published in English between January 2021 and December 2023, as shown in Fig. 1. The search strategy aimed to include all research articles, whether in vivo, in vitro, or clinical trial studies. Plant names were verified using the Plant List and Royal Botanical Garden, Kew databases. The search included the following keywords: Plants OR Phytotherapy OR Pharmacognosy OR Ethnopharmacology OR Dietary Phytochemical OR Plant Bioactive Compound OR Plant-Derived Chemical OR Bioactive Compounds OR Plant OR Phytonutrient OR extract OR leaves OR seeds AND Nephrolithiasis OR Urolithiasis OR Kidney Calculi OR Urinary Lithiasis OR Ureterolithiasis OR Urinary Calculi OR Ureteral Calculi OR Urinary Bladder Calculi OR Kidney stone AND Treatment OR Therapeutic OR Therapy OR Therapies OR Prophylaxis OR Preventive therapy OR Prevention OR Control.

Study selection

Two authors independently screened the titles and abstracts of all articles identified from the search. Full-text articles were then assessed for eligibility based on the inclusion

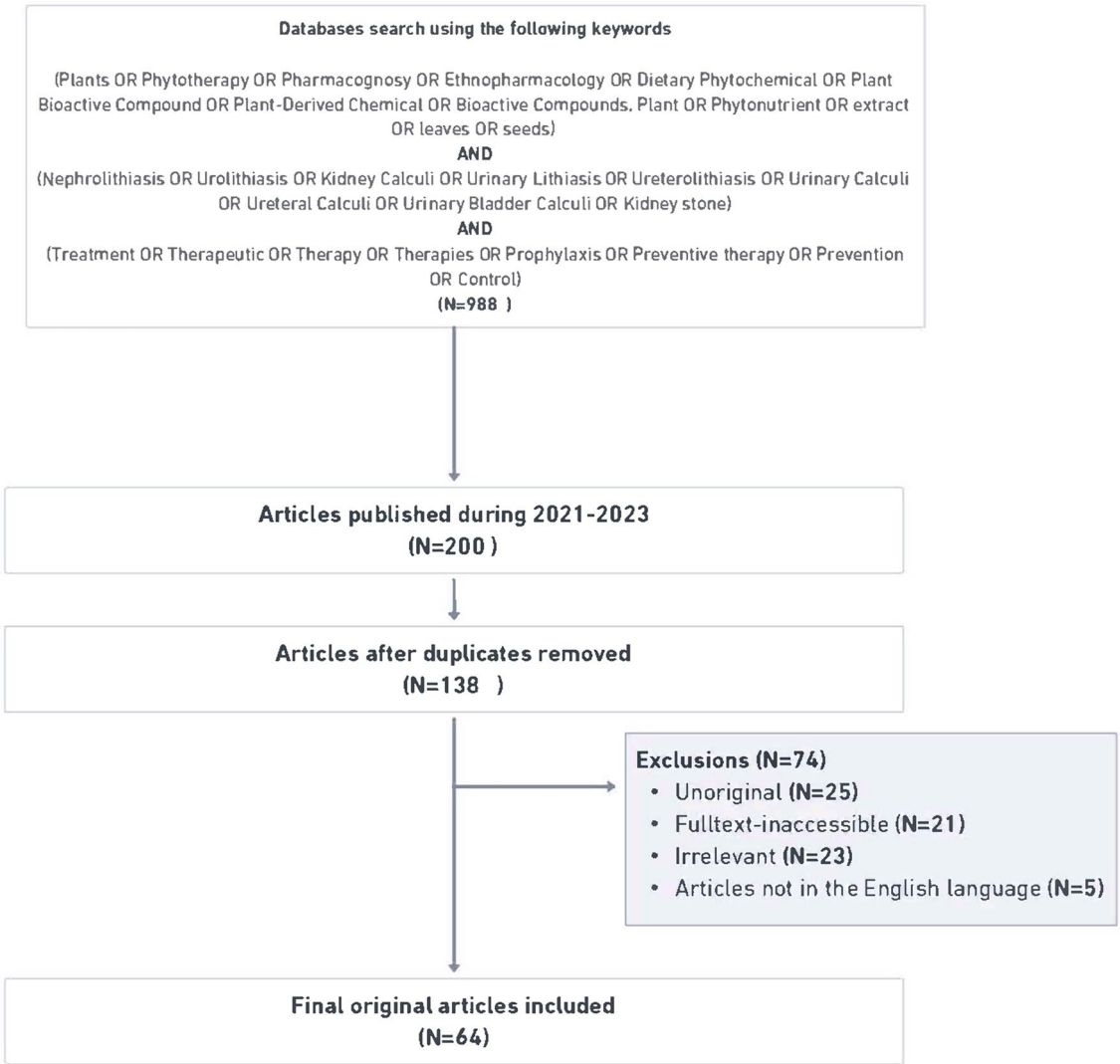


Fig. 1 Search parameters and criteria. The schematic illustration summarizes all keywords used for database searches and criteria to retrieve articles for discussion in this review

and exclusion criteria. Any disagreements were resolved through discussion. The inclusion criteria were studies that investigated the use of plants, dietary phytochemicals, phytotherapy, or plant bioactive compounds for the prevention or treatment of urolithiasis in in vivo, in vitro, or clinical trials. The exclusion criteria were non-original articles, duplicate publications, articles with inaccessible full text, irrelevant articles, studies focused on risk factors and mechanisms of urolithiasis without investigating anti-urolithic effects, and articles not in English.

Data extraction

Data extraction was performed independently by two authors using a standardized form. The extracted data included study design, type of stone, plant species, plant part used, solvent type, main findings, and study reference. Discrepancies were resolved through discussion. Data were analyzed using Microsoft Excel to summarize and synthesize the findings.

Data synthesis

Data were analyzed using the Excel program to summarize the data.

Results

The initial literature search used specified terms to identify 200 articles. After removing 62 duplicates, 138 articles remained. Upon further screening and reading, 21 articles were excluded due to the unavailability of full

text. Additionally, 53 articles were excluded as they were either review articles, not written in English, or focused on mechanisms of urolithiasis risk factors without investigating anti-urolithic effects. Ultimately, 64 publications were included in this systematic review.

Our review identified several studies that focused on different types of kidney stones, including calcium oxalate, uric acid, and infectious stones (struvite stones). The majority of studies investigated the effects of herbal treatments on calcium oxalate stones, which are the most common type. However, we also found evidence supporting the efficacy of herbal remedies in managing other stone types.

For instance, uric acid stones, which form in acidic urine, may be prevented by plant extracts that alkalinize the urine. Plants like *Cucumis melo var. inodorus* have shown potential in increasing urinary pH, thereby reducing the risk of uric acid stone formation [16]. Similarly, infectious stones, often associated with urinary tract infections, may benefit from the antimicrobial properties of certain herbs. For example, *Mentha piperita* has demonstrated antibacterial activity against common uropathogens, which can help prevent the formation of struvite stones [75].

The relevant information from all suitable articles was extracted and organized into tables and figures. The retrieved data encompassed details such as the study's methodology, the composition of the stone, the specific plant utilized, the plant part employed, the solvent type used for extraction, the nature of the study (in vivo, in vitro, clinical trial), the primary findings, and the study's reference.

Tables 1 and 2 demonstrate experimental signs on plants that prevent and treat urolithiasis in in vivo and in vitro studies, respectively. Table 3 exhibits clinical evidence of plants used to prevent and treat urolithiasis, while Table 4 summarizes the phytochemicals of different plants used for the same purpose.

Tables 1, 2, 3, and 4 present a comprehensive collection of pharmacological investigations on different types of extracts and formulations of medicinal plants and phytochemical substances, including aqueous, hydroalcoholic, alcoholic, and other varieties. The tables contain data on the cited study, the plant's scientific name, the specific plant part employed, the kind of extract, the type of stones, the crystal-inducing agent/model, and the anti-urolithic activity/mechanism. The herbal extracts were found to exhibit anti-urolithic actions, as evidenced by the following effects: decreased crystal deposition, reduced oxidative stress, improved renal morphology, changes in urinary pH, decreased levels of lithogenic factors in urine, such as oxalate, calcium, and phosphate, improved renal function, increased urinary citrate, and altered protein expression.

The majority of studies used 0.75–1% ethylene glycol (EG) in drinking water alone ($n=16$, 25%) [14, 16, 19, 22, 34] or in combination with ammonium chloride (AC) ($n=15$, 23.43%) [11–13, 18, 26] (Fig. 2) to provoke calcium oxalate (CaOx) nephrolithiasis. A small number of studies retained other methods, such as intraperitoneal injection of sodium oxalate (NaOx) in Wistar rats or Drosophila [21, 24], implantation of zinc disks into the bladder of rats [25], or feeding rats with 3% glycolic acid mixed with food for seven days [27]. Additionally, certain plants were the subject of multiple studies, in contrast to other plants, while the majority of stones utilized were CaOx ($n=54$, 84.4%) (Figs. 3 and 4).

The most common studies used aqueous extracts ($n=20$, 31.25%) [21–23, 42] and leaves ($n=23$, 35.9%) [12, 18, 20, 37, 44] were the widely utilized herbal preparations, as shown in Figs. 5 and 6. Other botanical parts utilized involved fruits ($n=6$, 9.4%) [13, 15, 22, 28], roots ($n=4$, 6.25%) [31, 57], tea preparation [46], peel and pulp [40], pits [42], citrus waste peel [49], seeds ($n=12$, 18.75%) [16, 19, 67], rhizomes [65], stems [14], and flowers ($n=4$, 6.25%) [29]. Some studies utilized whole plants ($n=18$, 28.1%) [21, 23, 24, 33, 35], herbal medications (Ningmitai capsule) [68], Daidzin (isoflavone compound) [70], and poly-herbal formulations such as Safoof-e-Pathar Phori [11].

Other extraction methods included hydroalcoholic ($n=7$, 10.9%) [15, 28, 30], methanolic ($n=10$, 15.6%) [17, 19, 20], or ethanolic solvents ($n=18$, 28.125%) [12, 13, 16, 18, 24, 29], although some studies applied formulations/constituents like triterpenoids extracted from plants [74] (Fig. 5). Numerous clinical trials have been conducted to explore the efficacy of various herbal treatments for urolithiasis. This systematic review inspected three clinical trials. In a randomized, single-blind clinical trial by Aryaeefar et al. (2022), a total of 126 patients with ureteral stones (0–10 mm) were randomly split into a control group and an intervention group that administered whole plant distillate of *Alhagi maurorum* for four weeks. Even though an insignificant difference in stone size or placement was detected between the groups, the time essential for stone removal was markedly shorter in the intervention group. Furthermore, a randomized, single-blinded study by Shakeri et al. (2022) evaluated the effects of *Nigella sativa* seeds and tamsulosin in 80 patients with kidney and ureteral calculi (4–10 mm). The two groups displayed a reduction in stone size and number, with a more considerable decrease in pain score noted in the *Nigella sativa* group. Wang et al. (2022) conducted a randomized clinical trial with 123 patients diagnosed with urinary stones (10–20 mm), where the Ningmitai capsule (a herbal formulation) group displayed significantly higher stone expulsion rates, stone-free rates, and shorter duration to complete a stone-free state compared to the control group.

The review systematically investigated six studies that searched the effects of plant-based compounds on kidney

Table 1 In vivo investigations on the therapeutic benefits of Medicinal Plants against urolithiasis

In vivo						
Plant	Part of the plant used	Study type	Type of stones	Study design	Main results	References
Safoof-e-Pathar Phori consisted of *(Didymocarpous pedicellatus R.Br* (Gesneriaceae), *Macrotyloma biflorum var. biflorum* (Leguminosae)*, Rheum webbianum Royle* (Polygonaceae), *Hordeum vulgare Linn. (Poaceae), Raphanus raphanistrum subsp. sativus* (L.) Domin (Brassicaceae*), and potassium nitrate)*	*Didymocarpous* leaves, *Macrotyloma* seeds, *Rheum* rhizome, *Hordeum* whole plant, and *Raphanus* whole plant finely powdered	In vivo	CaOx crystal	EG + AC-induced UL in male Wistar albino Rats	The application of treatment at dosages of 700 and 1000 mg/kg led to a notable reduction in Ca2+, serum creatinine (SCr), blood urea nitrogen (BUN) levels, and lipid peroxidation (LPO)	[11]
Platanus orientalis (Platanaceae)	Ethanolic extract of leaves	In vivo	CaOx crystal	EG + AC-induced UL in rats	Effectively, the extract reinstated the levels of Ca2+, citrate in the urine sample, superoxide dismutase (SOD) activity, and glutathione (GSH) levels in the kidney sample of the EG + AC group to their normal state. Simultaneously, it rectified the heightened levels of oxalate, myeloperoxidase, caspase-3, *N*-acetyl-β-D-glycosaminidase (NAG) activities, malondialdehyde (MDA), 8-hydroxy-2′-deoxyguanosine (8-OHdG), Tumor necrosis factor- alpha (TNF-α), and interleukine-1beta (IL-1β) in the kidney sample of the same group. Remarkably, a histo-pathological examination further demonstrated the extract's efficacy by indicating a regression of tubule expansion in both the cortex and medulla	[12]
Prunus cerasoides (Rosaceae)	The ethanolic extract of dried fruits	In vivo	CaOx crystal	EG + AC-induced UL in rats	The study observed ↑ in relative body weight, accompanied by a significant prevention of elevated urinary levels of Ca^{2+}, phosphate, oxalate, uric acid, and protein. Simultaneously, there were ↓ in the levels of Mg^{2+} and citrate. Interestingly, the study also found a mitigated ↑ in BUN, Cr, and uric acid serum levels. In addition, there was ↓ in kidney weight, tissue damage, inflammation, and tubular dilation	[13]
		In vitro		CaOx crystal in aqueous solution	The study observed a substantial ↓ in CaOx crystal size. Interestingly, crystals that were initially hexagonal or monoclinic calcium oxalate monohydrate (COM) transformed into octahedral-shaped calcium oxalate dihydrate (COD) crystals	

Table 1 (continued)

In vivo						
Plant	Part of the plant used	Study type	Type of stones	Study design	Main results	References
Ficus tikoua Bur. (Moraceae)	The stem extract	In vivo	CaOx crystal	EG-induced UL in rats	The study demonstrated restoring lymphocyte % in the blood and the concentration of salt, chlorine, and inorganic phosphates back to normal levels. Diuresis was maintained at the control level of the animals. Interestingly, no effect was observed on the urine urobilinogen concentration or ↑ in erythrocytes. However, the histo-pathological investigation did not indicate the efficacy of the treatment	[14]
Cucumis callosus (Rottl.) Cogn (Cucurbitaceae)	Hydro-ethanolic extract of fruits	In vivo	CaOx crystal	EG + AC-induced UL in rats	The study noticed ↓ urine oxalate levels, volume, and urinary urea nitrogen (UUN). Conversely, there was ↑ urine Ca^{2+} and pH. Furthermore, there was ↓ in BUN, Cr, and total protein. The study also observed ↓ the oxidant enzyme, lipid peroxidase, and ↑ GSH and catalase (CAT) levels. Furthermore, ↓ CaOx crystal deposition led to ↓ inflammation and renal damage in the hyperoxaluric rat kidney. Lastly, the study found ↓ the expression of osteopontin (OPN)	[15]
Cucumis melo var. inodorus (Cucurbitaceae)	Ethanolic extract of seeds	In vivo	CaOx crystal	EG-induced UL in rats	The study reported ↓ the kidney index, urinary Ca^{2+} and oxalate levels, CaOx deposits number and score, and the extent of histo-pathological damages. It was also observed ↓ in the inflammation score in the kidney sections. On the other hand, there were ↑ urinary pH, Mg^{2+}, and citrate levels. Furthermore, the expression of the spp1, UMOD, and reg1 genes in the kidneys of the treated animals was found to be elevated	[16]

Table 1 (continued)

In vivo						
Plant	Part of the plant used	Study type	Type of stones	Study design	Main results	References
Trachyspermum ammi (L.) (Apiaceae)	Methanolic extract of seeds	In vivo	CaOx crystal	EG + AC-induced UL in rats	The extract led to ↑ urine excretion of Na^+, although no substantial elevation was detected in the K^+ excretion. It halted the net loss in body weight, and both 24-h urine volume and water consumption were elevated. The extract considerably ↓ the urinary oxalate and restored the urinary Ca^{2+} to the average level. Interestingly, the urinary contents of citrate, phosphate, uric acid, and Mg^{2+} remained constant	[17]
		In vitro	CaOx crystal	CaOx crystal in aqueous solution	The study observed ↓ both slopes of nucleation and a concentration-dependent inhibition of crystal aggregation. There was also ↓ in CaOx crystal formation and size of COM. The study further noted an inhibition of lipid peroxidation, lactate dehydrogenase (LDH) release and DPPH-free radicals. Importantly, no toxic effects were observed on 2,2-diphenyl-1-picrylhydrazyl (MDCK) cells	
Calotropis procera (Apocynaceae)	Ethanolic extract of leaves	In vivo	CaOx crystal	EG + AC-induced UL in rats	The n-hexane fraction was used for in vivo research. The extract led to ↓ in blood Mg^{2+} levels and Mg^{2+}, Ca^{2+} urine levels compared to the control group. There was a considerable rise in Cr concentration but no noticeable variation in urea or uric acid quantities. A considerable elevation in the activities of alanine aminotransferase (ALT) and Aspartate aminotransferase (AST) was noted, along with ↑ the kidney GSH and SOD activity and ↓ kidney MDA	[18]
		In vitro	CaOx crystal	CaOx crystal in aqueous solution	The study observed a gradual ↑ in the inhibition of DPPH, with the highest values recorded in the n-hexane fraction. Notably, the n-hexane fraction of the extract demonstrated the most potent inhibitory effect on stone nucleation	

Table 1 (continued)

In vivo						
Plant	Part of the plant used	Study type	Type of stones	Study design	Main results	References
Peganum harmala L. (Nitrariaceae)	Methanolic extraction of seeds	In vivo	CaOx crystal	EG-induced UL in rats	In the treatment groups, there was a notable ↓ in serum toxicity indicators, such as BUN, Cr, urea, uric acid, Kidney Injury Molecule-1 (KIM-1), phosphate, Ca^{2+}, MDA, Mg^{2+}, and oxalate levels. Similarly, inflammatory markers, including TNF-α and nuclear factor kappa B (NF-κB), were downregulated in the kidney homogenate. Concurrently, urine production and urine pH were significantly ↑. The treatment facilitated a gradual recovery in the injured glomeruli, interstitial spaces, medulla, and tubules, accompanied by ↓ in brown calculi materials	[19]
Myrtus communis L. (Myrtaceae)	70% methanolic extract of leaves	In vivo	CaOx crystal	EG-induced UL in rats	The study found that the levels of various chemicals in the urine, including Ca^{2+}, Cr, Mg^{2+}, uric acid, citrate, and oxalate, were more aligned with those of the control group. Concurrently, water intake and urine output were ↓, while there was an ↑ in the body weights of rats when compared to the EG group. Despite noticeable tubular dilatation in the collecting tubules, as observed in hematoxylin–eosin staining, the sectional images bore more resemblance to the control group. In Pizzolato's staining, both the quantity and density of the crystals in the sections were ↓ in the extract group	[20]
Salvia miltiorrhiza (danshen) (Lamiaceae), *Astragalus* (Huang qi) (Fabaceae), *and Carthami flos* (HongHua) (Asteraceae)	Aqueous extracts of whole plant	In vivo	CaOx crystal	NaOx-induced UL in Drosophila model	The study demonstrated that the extracts indeed possess therapeutic benefits, which were notably more potent than those of nilutamide, luteolin, and quercetin	[21]
Ziziphus lotus (Rhamnaceae)	The aqueous fruit extract	In vivo	CaOx crystal	EG-induced UL in rats	The extract ↓ oxalate and Ca^{2+} in the urine primarily expels tiny COD crystals. This was accompanied by an ↓ in urine output. Notably, the crystalluria consisted of minimal COM particles. The dimensions of these crystals were ↓, leading to an ↓ in renal weight relative to the EG group	[22]

Table 1 (continued)

In vivo						
Plant	Part of the plant used	Study type	Type of stones	Study design	Main results	References
Astragalus membranaceus (Fisch.) (Leguminosae)	The aqueous extract of whole plant	In vivo	CaOx crystal	EG-induced UL in Drosophila model	The extract significantly ↓ the formation of CaOx crystals induced by EG, demonstrating a protective effect that extended the average survival days of Drosophila. However, in ex vivo tests, the extract did not impact the dissolution of CaOx crystals formed in the Malpighian tubule of Drosophila	[23]
Cyperus rotundus L. (Cyperaceae)	Ethanolic extract of the whole plant	In vivo	CaOx crystal	NaOx-induced UL in rats	The extract showed a significant ↓ in BUN, Cr, uric acid, urinary Na+, and chloride levels	[24]
		In vitro	CaOx crystal	CaOx crystal in aqueous solution	The research observed that ↑ the concentration of the extract was directly correlated with the inhibition of both crystal formation and aggregation	
Mimosa malacophylla (Fabaceae)	Methanolic extract of the aerial part	In vivo	CaOx crystal	Zinc disks- induced UL in rats	The extract did not induce any changes in the bladder, renal cortex, or medulla. Additionally, it did not trigger any cytotoxic activity or lead to morphological abnormalities in the nucleus of standard kidney cell lines	[25]
Mentha piperita L. (peppermint) (Lamiaceae)	The aqueous methanolic crude extract of fresh aerial parts	In vivo	CaOx crystal	EG + AC-induced Urolithiasis in rats	The extract ↑ urine output, Na^+ and K^+ excretion, and body weight. It also demonstrated a significant ↓ in the number of crystals and neutralized the acidic urine pH. The extract was significantly ↑ urinary Mg^{2+} and exhibited a notable ↓ in phosphate, uric acid, and total protein levels. It normalized Cr and BUN levels in a dose-dependent manner and restored MDA, GSH, and SOD levels. Moreover, the extract ↓ inflammation improved the integrity of the kidney epithelial membrane and normalized the interstitial gaps between cells	[26]
		In vitro	CaOx crystal	CaOx crystal in aqueous solution	The extract displayed antioxidant activity in a dose-dependent manner. Furthermore, the extract was observed to inhibit crystal nucleation, aggregation, and growth	

Table 1 (continued)

In vivo						
Plant	Part of the plant used	Study type	Type of stones	Study design	Main results	References
Caesalpinia bonducella (Caesalpiniaceae)	Ethanolic extract of seed	In vivo	CaOx crystal	EG, glycolic acid, and NaOx-induced different UL model	The extract treatment resulted in a significant ↑ in the body weight of the groups. Concurrently, there was a ↓ in the levels of urinary Ca^{2+} and phosphorus, while urinary Mg^{2+} levels saw an ↑. There was also an ↑ in urine volume, acidity, and pH levels. Blood biochemical markers, including uric acid, urea, Cr, BUN, and ALP, exhibited a notable ↓. The extract, supplied at dosages of 200 and 400 mg/kg, demonstrated that glomerular hypercellularity, casts and tubular hydropic degeneration were ameliorated in a dose-dependent manner in the kidney sections of the treated rats	[27]
Musa balbisiana (Musaceae)	Hydro-ethanolic extract from fruits	In vivo	CaOx crystal	EG-induced UL in rats	Histopathological evaluations revealed that the hydroethanolic extract treatment effectively counteracted the presence of CaOx crystal deposits in the renal tubules, as well as the congestion and dilation of these tubules. The extract also displayed diuretic properties, ↓ the growth of urinary stones, and led to an ↑ in the urinary excretion of Na^{+}, K^{+}, and Cl^{-}. At a high dosage of 1.6g/kg, there was a ↓ in urine Ca^{2+} levels and an ↑ in Mg^{2+} concentration. The high dosage also resulted in ↓ serum phosphate, Cr, and urea levels	[28]
		In vitro	CaOx crystal	CaOx crystal in aqueous solution	All extracts derived from the fruits of M. balbisiana demonstrated in vitro properties that ↓ the formation and aggregation of uric crystals, ↓ inflammation, combat microbes, and act as antioxidants. Among these extracts, the hydroethanolic extract obtained via heat extraction exhibited the most potent effects	
Hibiscus rosa-sinensis (Malvaceae)	Standardized ethanolic extract of flowers	In vivo	CaOx crystal	EG + AC-induced UL in rats	The extract showed an ↑ in urine volume, total protein, oxalate, phosphate, and uric acid concentrations, along with a ↓ in urinary excretion of Ca^{2+}, Mg^{2+}, and citrate. Histological studies revealed minimal damage and a ↓ in the amount of CaOx deposits in the kidney. However, sodium citrate proved more effective than *Hibiscus rosa-sinensis* (the extract at 600 mg/kg was more effective than at 300 mg/kg) in treating UL	[29]

Table 1 (continued)

In vivo						
Plant	Part of the plant used	Study type	Type of stones	Study design	Main results	References
Citrus medica, citrus limon and citrus Aurantium L (Rutaceae)	Hydroalcoholic extract of leaves of all three plants	In vivo	CaOx crystal	EG-induced UL in rats	The extracts showed a ↓ in urinary concentrations of Ca^{2+}, phosphate, Mg^{2+}, Cr, uric acid, protein, UUN, and oxalate, along with an ↑ in urinary output. A combined extract of all three plants, administered at a dose of 300 mg/kg, demonstrated a more substantial effect compared to the response from individual plant extracts	[30]
Aerva lanata (L.) (Amaranthaceae)	Ethanolic extract of roots	In vivo	CaOx crystal	EG-induced UL in rats	The extract returned body weight to normal levels, ↑ urine volume and pH, and ↓ the excretion of urinary components, such as Ca^{2+}, phosphorus, and oxalate. It also ↓ serum uric acid and Cr levels. Additionally, it ↓ crystal formation and size. Mild chronic interstitial inflammation was observed in both the conventional and extract therapy groups, with no signs of acute tubular damage. The group treated with a low dosage of the extract showed minimal signs of interstitial inflammation with lymphocytic infiltration. In contrast, the renal parenchyma of the group treated with a high dosage of the extract showed no significant pathological abnormalities, indicating that the 800 mg/kg extract mitigated kidney damage, thereby managing or preventing the disease	[31]
		In vitro	CaOx crystal	CaOx crystal in aqueous solution	The extract, at varying concentrations, significantly ↓ stone formation, as evidenced by an ↑ in the rate of absorbance. It also inhibited COM aggregation. Notably, a concentration of 100 µg/mL produced the lowest turbidity, greatest absorbance, and inhibited crystal formation	
Persea Americana (Lauraceae)	Methanolic seed extracts	In vivo	CaOx crystal	EG + AC-induced UL in rats	The research discovered that the extract led to a ↓ in average body weight, urine pH, and levels of urinary oxalate, Ca^{2+}, and Mg^{2+}. It also resulted in a ↓ in serum uric acid and Cr levels in the diseased groups. Furthermore, the extract was observed to ↓ the levels of acid phosphatase (ACP), alkaline phosphatase (ALP), AST, ALT, and LDH in kidney homogenate	[32]

Table 1 (continued)

In vivo						
Plant	Part of the plant used	Study type	Type of stones	Study design	Main results	References
Pyrrosia lingua (Polypodiaceae)	Ethanolic extract of the whole plant	In vivo	CaOx crystal	EG + AC-induced UL in rats	In the group treated with a high dose of the extract, blood Ca^{2+} and urine oxalic acid levels were ↓, while urine Ca^{2+} levels were ↑. In the moderate and low-dose extract groups, only urine Ca^{2+} and urine oxalate exhibited a ↓. The extract groups revealed a ↓ in the level of CaOx rat urine, indicating a dose-dependent impact. Nitric oxide levels were ↓, and SOD activity was ↑ in the renal tissues of rats in the low-dose extract group. In contrast, the levels of nitric oxide and MDA were ↓, while SOD activity was ↑ in the renal tissues of rats in the moderate and high-dose extract groups. The crystal deposits and degenerative scores were ↓ in the renal tissue of the rats in the extract groups in a dose-dependent manner. The expression of OPN was decreased in the kidney tissue and urine of rats in the extract groups, indicating a dose-dependent impact, with the high-dose extract group presenting the most significant changes. Furthermore, levels of *Bacteroidetes*, *Oxalobacter formigenes*, *Faecalibacterium*, and Bifidobacterium were noticeable ↓ following treatment with the extracts	[33]
Glechomae Herba (Lamiaceae) from 10 different regions	Ethanolic extract of the whole plant	In vivo	CaOx crystal	EG-induced UL in rats	The blood levels of Cr and BUN in rats administered the extract from various regions were significantly ↓ than those in the diseased group. The MDA concentration in the blood of all the extract groups was definitively ↓, while the CAT and SOD levels ↑ dramatically. The extract was effective in alleviating the dilation of renal tubules and inhibiting the infiltration of inflammatory cells. It also had a lower stone sedimentation score, indicating that the extract has an anti-inflammatory effect	[34]

Table 1 (continued)

In vivo						
Plant	Part of the plant used	Study type	Type of stones	Study design	Main results	References
Pyrrosia petiolosa (Polypodiaceae)	Ethanolic extract of the whole plant	In vivo	CaOx crystal	EG-induced UL in rats	The extract was found to significantly ↓ the levels of BUN, Cr, and Na^+ in serum, as well as 24-h oxalate, urinary protein, uric acid, Cr, Ca^{2+}, and phosphorus in the urine. It also ↑ the urine volume in rats in a dose-dependent manner, although it did not affect the urine pH. Additionally, the extract considerably mitigated EG-induced damage to renal tissue. The extract notably ↑ the levels of SOD and GSH, while ↓ the MDA level and the expression of NADPH oxidases 2 (NOX2) and NOX4 in kidney tissue. Additionally, in EG-stimulated kidney tissue, the extract dramatically decreased the levels of IL-1β, IL-6, TNF-α, and monocyte chemoattractant protein-1 (MCP-1). Additionally, in a concentration-dependent way, it suppressed the protein levels of EG-induced transforming growth factor-β1 (TGF-β1), p-Smad3, and p-Smad2	[35]
Gomphocarpus fruticosus (Asclepiadaceae)	Different solvents of the whole plant extract	In vivo	CaOx crystal	EG + AC-induced UL in rats	The ethyl acetate extracts significantly ↓ the level of Na^+, but it ↑ the levels of Mg^{2+} and citrate, compared to the lithiatic control group. The butanol extracts ↓ K^+, Ca^{2+}, and phosphate levels in urolithiatic rats. It was also found that the ethyl acetate extract ↓ the amount of oxalate in the urine, whereas the butanol extract ↑ the levels of Mg^{2+} and citrate in serum tests. CaOx crystal formations were remarkably ↓ by the ethyl acetate extract in the kidneys. Treatment with ethyl acetate and butanol extracts resulted in large ↓ urine protein excretions. The petroleum ether extracts ↑ the serum AST level considerably compared to the healthy control. The butanol extracts greatly ↓ the level of AST compared to the lithiatic control group	[36]

Table 1 (continued)

In vivo						
Plant	Part of the plant used	Study type	Type of stones	Study design	Main results	References
Origanum vulgare (OV) Linn (Lamiaceae)	Ethanol, aqueous and hexane extract of leaves	In vivo	CaOx crystal	EG + AC-induced UL in rats	In contrast to the untreated group, the treated group recovered from the extract right away. This was notably evidenced by weight gain and a significant ↓ in urinary oxalate, serum uric acid, urea, Cr, and renal crystal deposition. There was also an improvement in renal functions relative to the lithogenic group. Interestingly, the study indicated significant ↑ in blood pressure and heart rate in the EG + AC-treated group, but no significant changes were observed in both the extract and control groups	[37]
Dolichos biflorus (Fabaceae) and *Crataeva nurvala* (Capparidaceae)	*Dolichos biflorus* (D.b) (hydroalcoholic seed extract) and *Crataeva nurvala* (C.n) (aqueous bark extract) in two ratios 1:1 and 3:1	In vivo	CaOx crystal	EG + AC-induced UL in rats	The combination extracts significantly ↑ urine production compared to the UL group. When the urinary oxalate levels of rats treated with the combination extract were evaluated, in comparison to the values of the disease control group, there was no discernible difference. In the UL group, a higher Cr level was observed. Although in the standard and extract groups, it was elevated in the initial first two weeks, the findings were inconsequential ↓ in the last 2 weeks of the experiment. All the combination extracts appreciably ↓ the serum Ca^{2+} levels. In a 3:1 ratio, the glomeruli maintained the complete morphology of the glomerulus, and there was less injury to the tubules and other areas of the tissue	[38]
Argemone mexicana L. (Papaveraceae)	Methanol extract from leaves	In vivo	CaOx crystal	EG-induced UL in rats	Rats administered the extract showed steady ↑ body weight from the second week onwards, and their urine color transitioned from red to yellow. The extract-treated rats exhibited an ↑ in urine volume and pH. Additionally, there was a ↓ in serum Ca^{2+}, urea, and Cr levels in both male and female rats. The extract demonstrated a ↓ in crystal formation. The renal weight and size of the rats were ↓, and accumulated stones were eliminated with an ↑ in diuresis following exposure to the extract. The extract also repaired basophilic cells, degeneration cells, and regenerative cells	[39]

Table 1 (continued)

In vivo						
Plant	Part of the plant used	Study type	Type of stones	Study design	Main results	References
Cucumis melo L. (Cucurbitaceae)	Different solvent extracts of peel and pulp	In vivo	CaOx crystal	EG-induced UL in rats	Among all the peel extracts, the study discovered that even in comparison to the positive control, the chloroform and methanol extracts demonstrated a superior ability to ↓ renal calculi. Levels of serum Cr, uric acid, and BUN evidenced this. Conversely, only the chloroform extract showed a significant improvement in blood Cr and uric acid levels among all the pulp extracts	[40]
Cassia auriculata (Fabaceae)	Ethanolic extract of the whole plant	In vivo	CaOx crystal	EG + AC-induced UL in rats	Treatment with the extract was reported to provide a dosage-dependent anti-urolithiatic effect. This was evidenced by ↓ serum Ca^{2+}, Cr, and uric acid levels, along with an ↑ in urine volume. Additionally, there was a ↓ in urine Ca^{2+}, phosphate, and oxalate levels. SOD and CAT levels were ↑, coupled with a considerable ↓ in MDA levels	[41]
Date Palm (Phoenix dactylifera L.), (Arecaceae)	Aqueous extract of pits	In vivo	CaOx crystal	EG-induced UL in rats	The administration of date palm pit extracts in both the treatment and preventive groups at 300 mg/kg significantly ↓ the levels of BUN, uric acid, Ca^{2+}, Cr, and phosphorus. The urine data findings indicate that the extract administration led to a substantial ↓ in Cr, uric acid, and Ca^{2+} in the preventative group and a significant ↓ in Cr and uric acid in the therapy group with a dose of 300 mg/kg. The pathological findings indicate a dose-dependent decrease in the incidence and size of CaOx crystals in renal tubules in both the preventive and treated groups	[42]

LDH lactate dehydrogenase, *LPO*: lipid peroxidation, *MCP-1*: chemoattractant protein-1 (MCP-1), *MDA*: malondialdehyde, *NAC*: *N*-acetyl-β-D-glycosaminidase, *NF-κB*: nuclear factor kappa B, *OPN*: osteopontin, *SCr*: serum creatinine, *SOD*: superoxide dismutase, *TGF-β1*: transforming growth factor-β1, *TNF-α*: Tumor necrosis factor- alpha, *UL*: urolithiasis, *UUN*: urinary urea nitrogen

↑: increase/d, ↓: decrease/d, *8-OHdG*: 8-hydroxy-2′-deoxyguanosine, *AC*: ammonium chloride *ACP*: acid phosphatase *ALP*: alkaline phosphatase *ALT*: aminotransferase, *AST*: Aspartate aminotransferase, *BUN*: blood urea nitrogen, *CaOx*: Calcium oxalate, *CAT*: catalase, *COD*: calcium oxalate dihydrate, COM: calcium oxalate monohydrate, *Cr*: creatinine, *EG*: Ethylene glycol, *GSH*: reduced glutathione, *IL-1β*: interleukine-1beta, *KIM-1*: Kidney Injury Molecule-1

Table 2 In vitro studies on the therapeutic effects of Medicinal Plants against urolithiasis

In vitro						
Plant	Part of the plant used	Study type	Type of stones	Study design	Main results	References
Paronychia argentea lam (Rejel El-Hamama) (Caryophyllaceae), *Teucrium polium L.* (Jaa'deh) (Lamiaceae), *Alhagi maurorum Medik.* (Aqool" or "Shook El-Jamal) (Fabaceae), *Varthemia iphionoides A.P* (Ktilih" or "Shtilih) (Asteraceae), *Crataegus aronia L* (hawthorn or Zaroor) (Rosaceae)	Aqueous extract of aerial parts of *P. argentea*, *T. polium*, and leaves of *C. aronia, A. maurorum* roots, and *V. iphionoides* leaves and stems	In vitro	CaOx	CaOx crystal in aqueous solution	The study found that all plant extracts could inhibit nucleation, regardless of the dosage. Interestingly, the extract from V. iphionoides demonstrated the most potent aggregation inhibition at a low concentration	[43]
Alhagi maurorum (Boiss.), (Leguminosae)	Leaves aqueous extract	In vitro	CaOx	CaOx crystal in aqueous solution	The extract dissolved kidney stones, reduced pH to 5–6, and lessened stone mass	[44]
Alternanthera sessilis (Amaranthaceae)	The ethanolic extract of whole plant	In vitro	CaOx	CaOx crystal in aqueous solution	The extract efficiently catalyzed the mineralization of CaOx in a dose-dependent manner	[45]
Ononis spinosa L. (Fabaceae)	The root is used as a crumbled herb for tea preparation	In vitro	Various kidney stones from patients	Various kidney stones in *O. spinosa* extract solution	Spectrophotometric analysis revealed a statistically significant passage of Ca2+, phosphate, and uric acid through the tea preparation solution	[46]
Enhydra fluctuans Lour. (Asteraceae)	The aqueous extract of whole plant	In vitro	Calcium phosphate crystals	Ca phosphate crystal in aqueous solution	The extract exhibited inhibitory effects on the development of brushite crystals, ↓ the average length of deposited brushite crystals and demonstrated antibacterial and antioxidant properties	[47]
Melia azedarach L. (Meliaceae)	Chloroform, Methanolic and aqueous extract of fruit-seeds	In vitro	CaOx	CaOx crystal in aqueous solution	All the extracts exhibited an ↑ in value for the incubation time ↑. The chloroform extract was more potent than methanol and aqueous extracts in dissolving Ca2+ crystals and nucleation assay	[48]

Table 2 (continued)

In vitro						
Plant	Part of the plant used	Study type	Type of stones	Study design	Main results	References
Citrus limetta, Citrus limon and Citrus sinensis (Rutaceae)	Hexane, aqueous and ethanol extract of citrus waste peel	In vitro	CaOx	CaOx crystal in aqueous solution	The ethanolic extract of C. sinensis peels significantly suppressed CaOx nucleation, growth, and aggregation at a concentration of 1000 µg/mL, demonstrating superior efficacy compared to other solvents and plants	[49]
Bryophyllum pinnatum (BPE) (Crassulaceae) and *Macrotyloma uniflorum* (MUE) (Fabaceae)	Hydroalcoholic extracts of leaves and seeds of BPE and MUE, respectively	In vitro	COM crystal	COM crystal-injured cells	The extracts significantly ↑ Vero cells viability that were exposed to COM crystal in a dose-dependent manner, showing maximal efficacy at 200 µg/ml. Macrotyloma uniflorum exhibited superior wound healing efficacy than BPE. Additionally, the extracts demonstrated antioxidant activity	[50]
Drymoglossum piloselloides (Polypodiaceae), *Aegle marmelos* (Rutaceae) and *Kalanchoe* (laciniata Crassulaceae)	The aqueous, ethanol, and hexane extracts of *Drymoglossum piloselloides* leaves, *Kalanchoe laciniata* leaves, and *Aegle marmelos* flowers	In vitro	CaOx crystal	CaOx crystal in aqueous solution	All the extracts exhibited a dosage-dependent ability to inhibit the nucleation, growth, and aggregation of CaOx crystals	[51]
Basella rubra (Basellaceae)	The hydroalcoholic extracts of leaves and stem pod	In vitro	CaOx crystal	CaOx crystal in aqueous solution	The extracts demonstrated a significant ↓ in the weight of the CaOx tablet, and the stem pod extract has the highest percentage solubility of the tablet	[52]
The tea bag was composed of *(Dolichos biflorus* (Fabaceae*), Phyllanthus emblica L.* (Euphorbiaceae*), Ocimum tenuiflorum L.* (Lamiaceae), *Green Tea, Withania somnifera* (Solanaceae), *Foeniculum vulgare Mill.* (Apiaceae) and *Stevia* (Asteraceae))	Aqueous extract of Seeds, fruit, leaves, leaves, root powder, Seed powder, and leaves, respectively	In vitro	CaOx crystal	CaOx crystal in the urine of healthy subjects	Smaller crystals and a decrease in crystal density were the results of increasing dosages of the study formulation. A dose-dependent % inhibition was detected in the DPPH assay, indicating antioxidant activity in both the reducing power assay and hydrogen peroxide scavenging activity	[53]

Table 2 (continued)

In vitro						
Plant	Part of the plant used	Study type	Type of stones	Study design	Main results	References
Bryophyllum pinnatum (Crassulaceae) and *Aerva lanata* (Amaranthaceae)	Ethyl acetate extract of Fresh leaves of *Bryophyllum pinnatum* and flowers of *Aerva lanata*	In vitro	CaOx crystal	CaOx crystal in aqueous solution	The maximum dissolution of CaOx was observed in the extract of *Bryophyllum pinnatum* at a concentration of 10 mg, which may be attributed to Bufadienolides rather than *Aerva lanata*	[54]
Saussurea costus (Falc) Lipsch (Asteraceae)	Aqueous and Ethanolic extract of roots	In vitro	Cystine stone and CaOx crystal	Cystine stone and CaOx crystal in aqueous solution	The dissolution of cystine stones ↑ over time, from the first to the last week, with the aqueous extract showing the most significant effect. The dissolution process was independent of the cystine calculi's pH for the ethanolic extract. This plant's ethanolic extract significantly inhibited the crystallization of CaOx. The ethanolic extract had the greatest IC50, according to the DPPH technique, with a value of IC50 = 0.12325 mg/ml. However, the FRAP method showed that the aqueous extract, with a 300 µg/ml concentration, possessed the most excellent reducing power	[55]
Garcinia humilis (Cluciaceae)	Methanolic, dichloromethane, and ethyl acetate fractions obtained from the leaves	In vitro	CaOx crystal	CaOx crystal in urine	All the different preparations could produce an anti-urolithic action in vitro and ↓ the quantity of COM and COD crystals	[56]

Table 2 (continued)

In vitro						
Plant	Part of the plant used	Study type	Type of stones	Study design	Main results	References
Pleurolobus gangeticus (L.) J. St.- Hil. ex H. Ohashi & K. Ohashi (Fabaceae)	Chloroform extract of fresh roots	In vitro	CaOx crystal	In vitroCaOx crystal	The findings showed that the production of CaOx crystals was impacted in a dose-dependent manner by the chloroform fraction. The maximum dose of 10 mg/mL in both nucleation and aggregation studies demonstrated superior results. This concentration resulted in considerable ↑ in CaOx crystal nucleation, a reduction in crystal size and the suppression of crystal aggregation	[57]
Sida acuta Burm. F. (Malvaceae)	Ethanolic extract of leaves	In vitro	Struvite crystal	Struvite crystal hydrogel medium	The extract, at various dosages, significantly ↓ the average weights of struvite crystals in a dose-dependent manner	[58]
Orthosiphon stamineus (Lamiaceae)	The standardized water extract of the whole plant in different concentration	In vitro	CaOx and uric acid stones	Stones from patients immersed in the plant extract solution	The maximum percentage weight decreases of CaOx stone occurred at a dosage of 4 mg/ml. The *O. stamineus* extract at 4 mg/ml demonstrated a more significant chemolytic activity on CaOx stone than the potassium citrate solution, with 70% effectiveness at pH 5, 48% at pH 7, and less than 10% at pH 8. The percentage weight decrease of uric acid stones was found to be 47%, 11%, and 14% at pH 5, 7, and 8, respectively. The data analysis demonstrated that the % weight reductions of combination stones differed considerably across acidic, neutral, and alkaline conditions	[59]

Table 2 (continued)

In vitro						
Plant	Part of the plant used	Study type	Type of stones	Study design	Main results	References
Herniaria hirsuta L. (Caryophyllaceae), *Opuntia ficus-indica* (Cactaceae), *Zea mays* (Poaceae) and *Ammi visnaga L* (Apiaceae)	Aqueous extract of *H. hirsuta L.*, fully used (leaves and stems), *O. ficus-indica* flowers, *A. visnaga L.* seeds and very fine filaments that come from the outer shell corn cobs *Z. mays* styles	In vitro	CaOx crystal	In vitro CaOx crystal in extract solution	The comparison of the stone dissolution rates for the four plants suggests that Zea mays may exert a slightly more pronounced effect than the others	[60]
Ocimum sanctum (Lamiaceae)	Hydroalcoholic extract of leaves	In vitro	CaOx crystal	CaOx crystal solution	A 40.32% suppression of CaOx nucleation was reported with the extract's maximal concentration (8 mg/ml). Microscopic analysis showed that the extract decreased the number and size of crystal nuclei as concentration increased. The highest aggregation inhibition (33.9%) was seen at a dosage of 1 mg/ml. Significant suppression of crystal growth was reported at 1 mg/ml and 2 mg/ml of the extract, with 94.59% and 97.21%, respectively	[61]
Phyllanthus niruri L. (Phyllanthaceae)	Different solvent leaves extract	In vitro	CaOx crystal	CaOx crystal solution	The methanolic extract exhibited the highest inhibition against the aggregation of CaOx crystals. The aqueous extract was shown to be more effective in the dissolution of CaOx. The nucleation rate, aggregation of CaOx crystallization, and crystal density were all markedly inhibited by *P. niruri*	[62]

Table 2 (continued)

In vitro						
Plant	Part of the plant used	Study type	Type of stones	Study design	Main results	References
Rhus chinensis Mill. (Anacardiaceae)	Aqueous extract of leaves	In vitro	CaOx crystal	CaOx crystal solution	The water extract greatly ↓ the rate of nucleation and aggregation of CaOx crystallization and ↓ the crystal density in a way dependent on both time and concentration	[63]
Costus spicatus (Jacq.) Sw. (Costaceae)	Ethanolic extract of leaves at different concentrations	In vitro	CaOx crystal	CaOx crystal in human urine	The extract had a concentration-dependent effect on urinary crystallization, reducing the size and percentage of monohydrated crystals	[64]
Bergenia ligulata (Wall.) (Saxifragaceae)	Different solvent extracts of dried rhizome	In vitro	CaOx crystal	CaOx crystal solution	The ethanolic extract (200 µg/mL) demonstrated the maximum suppression in nucleation and aggregation experiments. This extract also enhanced cell vitality in a dosage-dependent manner, with the highest viability observed in cells treated with 200 µg/mL. Notably, there was a considerable change from thermodynamically stable COM crystals to less damaging COD crystals	[65]

↑: increase/d, ↓: decrease/d, *CaOx*: Calcium oxalate, *COD*: calcium oxalate dihydrate, *COM*: calcium oxalate monohydrate

Table 3 Clinical trial research on the therapeutic efficacy of Medicinal Plants on urolithiasis

Clinical trial						
Plant	Part of the plant used	Study type	Type of stones	Study design	Main results	References
Alhagi maurorum (Leguminosae)	Whole plant distillate	A randomized, single-blind, clinical trial	Not identified	In the study, 65 patients were randomized to the control group, while 61 were assigned to the intervention group. These individuals, all aged over 18 years, were presented with symptoms of renal colic due to ureteral stones measuring 0–10 mm. The patients were administered the distillate for four weeks	No significant difference was observed in the intervention and control groups' demographic parameters, stone size, and placement. However, the time required for removal was notably shorter in the intervention group	[66]
Nigella sativa (Ranunculaceae)	Intact seeds capsule	Randomized single-blinded clinical trial study	Not identified	A study was conducted on 80 adult patients, each presenting with kidney and ureteral calculi measuring 4–10 mm. These individuals, who exhibited no symptoms necessitating immediate intervention or significant discomfort, were recruited from a urology clinic The patients were subsequently divided into two distinct groups. The first group was administered a daily dosage of 0.4 mg of tamsulosin. Conversely, the second group received 2g of encapsulated Nigella sativa seeds daily	Before treatment, no significant difference was observed between the two groups. However, post-treatment, both groups exhibited a reduction in the size and number of stones per patient. The average pain score before therapy was comparable between the two groups. Following the intervention, a considerable ↓ in pain score was noted in both groups, with a more significant reduction in the *Nigella sativa* group In terms of treatment efficacy, the two subjects' combined whole and fractional responses approached 60%. Nevertheless, substantial differences were observed between the two groups	[67]

Table 3 (continued)

Clinical trial						
Plant	Part of the plant used	Study type	Type of stones	Study design	Main results	References
Ningmitai capsule composed of (*Herba Polygoni Capitati* (Polygonaceae), *Rhizoma Imperatae* (Gramineae), *Radix Cocculi Trilobi* (Menispermaceae), *Fructus Forsythiae suspensae* (Oleaceae), *Berberidis radix* (Berberidaceae), *Herba Agrimoniae* (Rosaceae) and, *Folium Hibisci Mutabilis* (Malvaceae))	Ningmitai capsule	Randomized clinical trial study	Not identified	Patients within the age range of 18–60 years were diagnosed with upper urinary tract stones, with sizes varying from 10 to 20 mm. The diagnostic methods employed were Intravenous Pyelography/Computed Tomography Urography (IVP/CTU) and non-contrast Computed Tomography (CT). One hundred twenty-three patients were randomly assigned to two groups: the Ningmitai capsule group (63 patients) and the control group (60 patients)	The cumulative expulsion rates of stones on the 3rd, 7th, 14th, and 28th days were significantly elevated in the group treated with Ningmitai capsules compared to the control group. Furthermore, the stone-free rates on the 14th and 28th days were markedly higher in the Ningmitai capsule group. The average duration to achieve a stone-free state was shorter in the Ningmitai capsule group relative to the control group. On day 14, the urine white blood cell (WBC) counts in the Ningmitai capsule group were significantly lower than in the control group A total of 11 adverse events were reported in 8 patients, which included five instances of hematuria, 1 instance of fever, 2 instances of pollakiuria, 2 instances of renal colic, 1 instance of renal subcapsular hematoma, and 1 instance of low backache. All affected patients experienced spontaneous recovery, and no significant difference in the incidence of adverse events was observed between the two groups	[68]

↓: decrease/d

Table 4 Therapeutic Effects of Phytochemicals on Urolithiasis

Phytochemical	Part of the plant used	Study type	Type of stones	Study design	Main results	References
Quercetin Betulin	Flowers of *Aerva lanata* (Amaranthaceae)	In vivo	CaOx crystal	EG-induced UL in rats	The administered components significantly ↑ both the weight of the rats and their urine output. Concurrently, a ↓ in the formation of calculi was observed in the renal tissue. Serum analysis revealed significant ↓ in levels of BUN, uric acid, and Cr. Histopathological evaluations indicated an ↑ in the anatomical structure of the renal tissue. Animals treated with the test drug in combination with piperine exhibited substantial ↓ in levels of Ca^{2+}, phosphate, and oxalate crystals compared to both the diseased animals and those treated with the test drug alone	[69]
Daidzin	Not identified	In vivo	CaOx crystal	EG-induced UL in rats	Daidzin therapy effectively ↓ the urine pH and protein levels, while ↑ the urine volume in the UL rats. This was accompanied by a significant ↓ in the urine crystal score. Daidzin also ↓ the levels of Ca^{2+}, oxalate, uric acid, urea, Cr, and BUN, while ↑ the levels of Mg^{2+} and phosphorus in the UL rats. The activities of ALT, AST, ALP, gamma-glutamyl transferase (GGT), and LDH in serum and renal tissue were successfully ↓ by Daidzin. Additionally, Daidzin ↓ the levels of TNF-α and adiponectin, ↑ the antioxidant levels (SOD, Glutathione Peroxidase (GPx), GSH), and ↓ LPO. Microscopic examination revealed relatively few calcified structures and no degeneration of glomeruli in the kidney	[70]
Trigonelline	Not identified	In vitro	COM crystal	COM crystal in solution, Madin-Darby canine kidney, the renal tubular epithelial cell line	The findings indicated that trigonelline significantly ↓ the number, size, and mass of COM crystals during crystallization. Trigonelline reduced crystal growth and cell adhesion in a dose-dependent manner but did not influence crystal aggregation. Trigonelline treatment led to a decrease in the amount of COM crystal receptors on the apical membranes, as confirmed by mass spectrometry protein identification. Trigonelline therapy led to decreased levels of some crystal receptors, as validated by Western blotting analysis	[71]

Table 4 (continued)

Phytochemical	Part of the plant used	Study type	Type of stones	Study design	Main results	References
Medicagenic acid	An aqueous extract of the aerial parts of *Herniaria hirsuta L.* (Caryophyllaceae)	In vitro	COM crystal	COM crystal in solution, Madin-Darby canine kidney, the renal tubular epithelial cell line	The results from the crystallization assay revealed that there was no significant impact on either the nucleation or aggregation phase. However, the crystal–cell interaction experiment showed considerable ↓ differences in crystal binding	[72]
Methyl gallate (MG) and gallic acid (GA)	From *Mimosa bimucronata* leaves (Fabaceae)	In vitro	CaOx crystal	CaOx crystal in solution	The GA compound suppressed around 44–57% of the overall production of CaOx crystals, whereas the MG compound inhibited around 48.35%. Exposure to both GA and MG hindered COM formation. Additionally, these chemicals ↓ the absorbance in urine specimens, which is associated with a reduction in CaOx aggregation and precipitation	[73]
Pentacyclic triterpenoids (Lupeol and Ursolic acid)	Fresh leaves of *Alstonia scholaris* (Apocynaceae)	In vivo	CaOx crystal	EG + AC-induced UL in rats	The components ↓ nitrogenous wastes, such as Cr, uric acid, BUN, TNF-α, and IL-6. Additionally, they ↓ levels of crystallization promoters like Na^+, K^+, Cl^-, Ca^{2+}, oxalate, and phosphorus. The treatment ↑ urine volume and ↓ kidney weight. Microscopic examination of urine revealed the absence of stag horn calculi. MDA levels were ↓, while SOD, GSH, and CAT levels were ↑. Kidneys from the treatment group exhibited normal morphology with no crystal accumulation	[74]

↑: increase/d, ↓: decrease/d, *AC*: ammonium chloride, *ALT*: aminotransferase, *AST*: Aspartate aminotransferase, *BUN*: blood urea nitrogen, *CaOx*: Calcium oxalate, *CAT*: catalase, *COM*: calcium oxalate monohydrate, *Cr*: creatinine, *EG*: Ethylene glycol, *GGT*: glutamyl transferase, *GPx*: Glutathione Peroxidase, *GSH*: reduced glutathione, *IL-6*: interleukine-6, *LDH*: lactate dehydrogenase, *LPO*: lipid peroxidation, *MDA*: malondialdehyde, *SOD*: superoxide dismutase *TNF-α*: Tumor necrosis factor- alpha, *UL*: urolithiasis

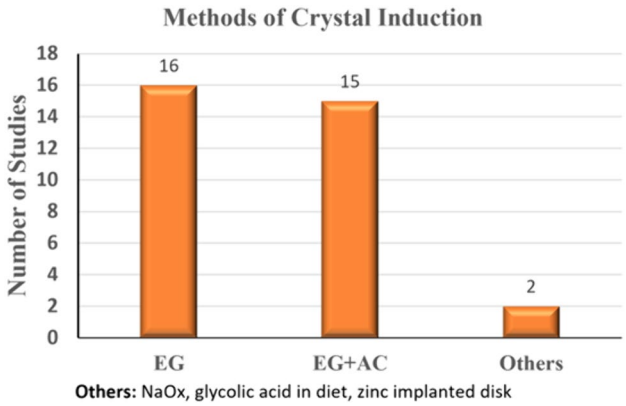


Fig. 2 Number of studies based on the methods used for crystal induction. *NaOx* sodium oxalate, *EG* ethylene glycol, *AC* ammonium chloride

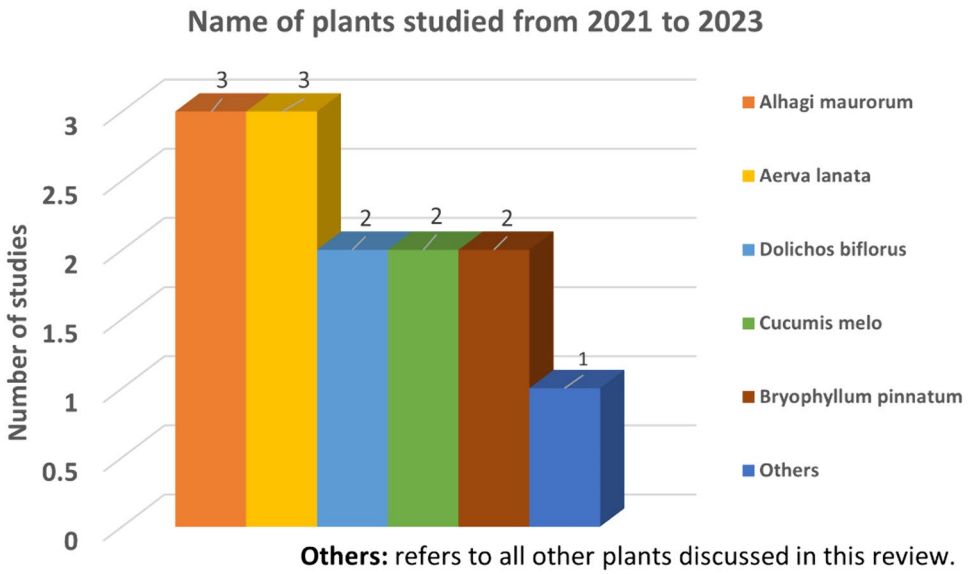
stones. These studies used in vitro and in vivo methods to investigate the impact on CaOx and calcium oxalate monohydrate (COM) crystals. The compounds examined included Quercetin, Daidzin, Trigonelline, Medicagenic Acid, Methyl Gallate, Gallic Acid, and Pentacyclic Triterpenoids (Lupeol and Ursolic acid). The studies' results showed the effects of these substances on the development of stones, including alterations in urine characteristics, such as urine output volume, pH levels, protein concentrations, crystal features, such as size, number, and mass, as well as changes in levels of other biochemical markers. In rat models with CaOx nephrolithiasis circumstances were associated with modifications in components like oxalate and citrate levels together with variations in pH balance, oxidative stress markers, production of crystallization modulators and inflammatory molecules, Crystal formations in urine and deposition within the kidneys [12, 15]. Most studies have revealed enhancements in renal structure and function following the administration of these compounds. Moreover, it was frequently noted in the research that there were changes in the excretion levels of CaOx, magnesium, and phosphate.

Discussion

Nephrolithiasis, or the development of kidney stones, is a complex and multifactorial process that involves several steps and physicochemical changes in the urine environment. These changes result in the production of crystals, their growth, aggregation, and subsequent retention inside the kidneys [76, 77]. This process concerns interactions between many urinary ions and a range of crystallization modulatory macromolecules. Most idiopathic CaOx stones develop on a base of biological apatite called Randall's plaque (RP). This plaque starts in the renal papillary interstitium and travels outward to the papillary surface. When the surface epithelium breaks down, the plaque becomes exposed to the urine in the pelvic area. Furthermore, some stones form joined to tubular crystal deposits, struggling the terminal collecting ducts [78, 79].

Herbal treatments can complement lifestyle changes by targeting specific pathways involved in stone formation. For example, many phytochemicals have anti-inflammatory and antioxidant properties that can mitigate the renal damage caused by oxidative stress, which is not directly addressed by lifestyle modifications [80]. Furthermore, some herbal remedies have diuretic and antispasmodic effects, which can aid in the expulsion of stones and provide symptomatic relief [81].

Fig. 3 Number of studies discussed a certain plant name from 2021 to 2023



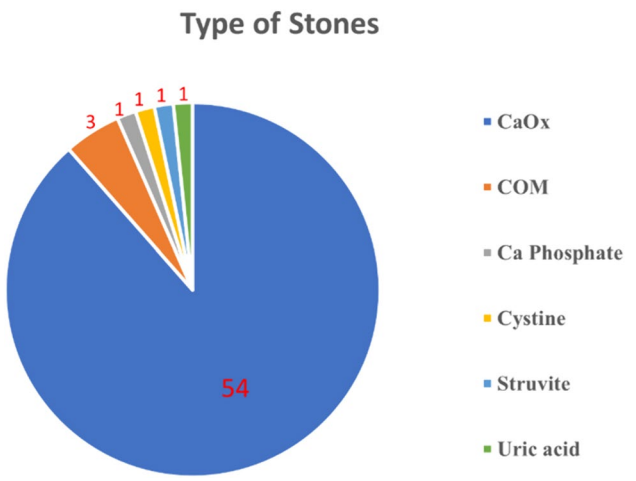


Fig. 4 Number of studies based on the types of stones studied. *CaOx* calcium oxalate, C*O*M calcium monohydrate

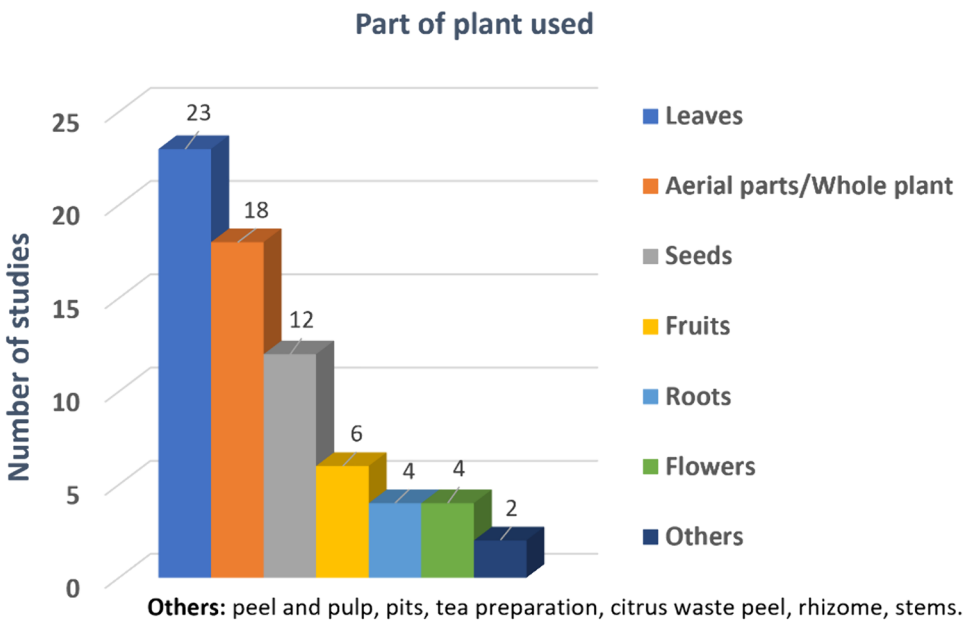
To investigate the pathogenesis of CaOx nephrolithiasis and develop therapeutic agents, various in vitro and in vivo models have been established [82, 83]. CaOx crystal nucleation, growth, and aggregation were investigated in vitro crystallization studies with and without crystallization modulators [51]. These methods afford a preliminary evaluation of crystallization modifying activity, probable modes of action, and anti-urolithic potential. Nonetheless, the biological system and pathogenesis of urolithiasis are complicated, and these in vitro results cannot be extrapolated to therapeutic effects [84].

As a result, in vivo animal models of CaOx nephrolithiasis have been established to understand the pathophysiology better and examine the anti-urolithic activities and potential of various medicines [29, 30]. Experimental nephrolithiasis is induced by administering hyperoxaluria-inducing agents through drinking water, diet, or injection [85, 86]. These in vivo models have considerably contributed to our understanding of human illnesses and remain a key tool for researchers to examine numerous physiological processes, biochemical events, and test novel pharmaco-therapeutic drugs [87].

The majority of the studies reviewed here have utilized the well-established and relatively economical rat model of nephrolithiasis by administering EG in drinking water, either alone [19, 20] or in combination with AC [15, 18]. EG, a precursor of oxalic acid, is quickly absorbed from the gastrointestinal system and converted to oxalic acid by hepatic enzymes. EG predominantly affects the kidneys, with substantial variations in sensitivity among strains, species, and sexes. In comparison to mice, rats are more sensitive, and male rats are more sensitive than female ones. While EG (0.75–1%) alone can induce CaOx deposition, its effects are variable [88]. In order to decrease the amount of time needed and attain a consistently high rate of renal crystal deposition, hypercalciuric, nephrotoxic, or pH-reducing procedures, such as AC [89], gentamicin [90], or a diet lacking in magnesium, has been combined with EG.

When rats are given EG at a concentration of 0.75% or more in drinking water, they develop hyperoxaluria, which leads to crystalluria and CaOx crystal deposition in the renal tubules [28]. The incidence of crystal deposition in the kidney varies from 80 to 100%, depending on the co-administered medicine, and nephrolithiasis develops in around 1–3 weeks [91]. Oxidative stress in the kidneys, increased water intake and polyuria, lower urinary pH, decreased urinary Ca2+, Mg2+, and citrate contents,

Fig. 5 Number of studies based on parts of the plants used



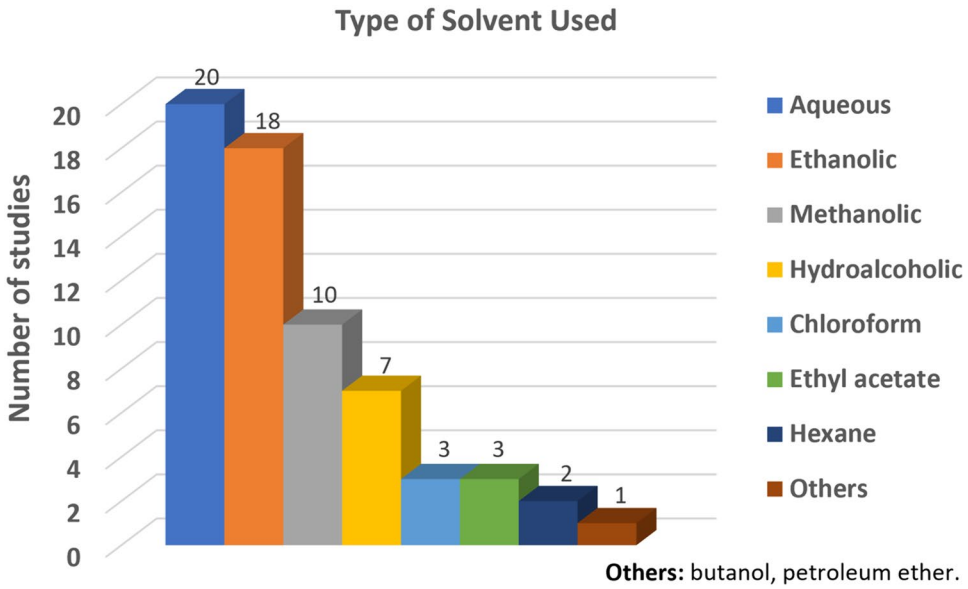


Fig. 6 Number of studies based on the types of solvents used in the extraction

increased CaOx crystalluria, phosphate excretion, renal hypertrophy, and weight loss are the main characteristics of hyperoxaluria-induced nephrolithiasis [35, 39]. Increased loss of urine protein, decreased clearance of creatinine, and raised levels of blood urea nitrogen (BUN) and creatinine in the serum are further indicators of renal impairment [30, 34].

Herbal therapies were prepared for assessment using a variety of plant parts in the examined research, including flowers, seeds, fruits, leaves, stems, roots, and rhizomes. The most popular component was leaves, which were extracted using alcoholic, hydroalcoholic, and aqueous solvents. The effectiveness of herbal administration was evaluated in relation to common biomarkers of nephrolithiasis, including renal CaOx crystal deposits, citrate, pH, oxalate, oxidative stress markers, urine calcium, phosphate, and improved renal structure and function. While some studies did not investigate every facet of nephrolithiasis, every therapy decreased the amount of CaOx crystals that were deposited in the kidneys. Most studies indicated that using herbal remedies improved the kidneys' structure and function. Furthermore, research on oxidative stress showed that herbal remedies have antioxidant qualities.

The clinical trials in this review suggest potential benefits of herbal treatments like *Alhagi maurorum*, *Nigella sativa*, and the Ningmitai capsule (a Chinese herbal formulation) in facilitating stone passage, alleviating pain, promoting stone expulsion, and increasing stone-free rates in patients with urolithiasis. While these findings corroborate the traditional use of these herbs and provide preliminary evidence for their anti-urolithic properties, the number of trials is limited. Larger, well-designed clinical studies are warranted to further evaluate the efficacy and safety of these herbal treatments, including their potential interactions with conventional therapies, before recommending their use in clinical practice.

The studies investigating various phytochemicals highlight their potential as therapeutic agents for urolithiasis. Quercetin, Daidzin, trigonelline, medicagenic acid, methyl gallate, gallic acid, lupeol, and ursolic acid exhibited anti-urolithic effects by reducing crystal formation, adhesion, aggregation, and oxidative stress while improving renal function in experimental models. These findings suggest phytochemicals may target multiple pathways involved in stone formation and associated renal dysfunction. However, further research is warranted to elucidate their mechanisms of action, optimize dosing and formulations, evaluate safety profiles, and translate these findings into clinical applications to prevent and manage urolithiasis.

Differentiating between stone types is crucial for effective management. Herbal treatments can be tailored to target the specific pathophysiological mechanisms of different stones. For calcium oxalate stones, phytochemicals, such as quercetin and gallic acid, can inhibit crystal formation and aggregation. For infectious stones, the antimicrobial properties of herbs like *Mentha piperita* can help prevent stone formation by controlling urinary infections. This targeted approach allows for a more personalized treatment plan, potentially improving outcomes for patients with different types of kidney stones.

In conclusion, this systematic review critically evaluates the use of various phytochemical and natural herbal treatments in experimental models of nephrolithiasis, highlighting their potential as therapeutic agents for managing this complex condition. The findings underscore

the need for further research to elucidate the underlying mechanisms and translate these findings into clinical practice.

Conclusion

This systematic review has provided a comprehensive overview of the current state of research on the use of plants in treating and preventing urolithiasis. The findings suggest that various plants and their components have significant potential in managing this condition. They reduce the size and number of stones and alter the levels of urinary oxalate, calcium, phosphate, and citrate, which are critical factors in stone formation. However, further well-designed clinical trials are needed to validate these findings and establish these plants' optimal use in clinical practice. This research opens new avenues for developing safe and effective phytotherapeutic strategies for urolithiasis, and ongoing research is essential to translate these findings into clinical applications.

Author contributions E.A.H.A was responsible for the conceptualization of the study, developing the methodology, and overseeing the data curation process. Essmat conducted the formal analysis and investigation, prepared the original draft of the manuscript, and contributed significantly to the review and editing process. Additionally, Essmat handled the visualization of data, supervised the project, and managed the overall project administration. M.S. contributed to the data curation and formal analysis, participated in the investigation, and assisted in the review and editing of the manuscript. Mahmoud also contributed to the visualization of the data.

Funding No specific grant was received by this study from any commercial, not-for-profit sectors, or public funding agencies.

Data availability The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval Not applicable.

Consent for publication Not applicable.

Institutional review board statement Not applicable.

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