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A review on herbal drugs in the management of Urolithiasis

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Abstract
Kidney stone is a common and painful condition affects millions of people worldwide. Due to the side-effects of synthetic medicines, herbal drugs are considered as a remedy for kidney stone. This review aims to summarize the importance of herbal medicines for the treatment of kidney stone. A vast literature search was conducted to study about the herbal extracts and compounds for the antiurolithic activity. These herbal extracts have the ability to inhibit calcium oxalate stones, primary reason for kidney stone. Many medicinal plants including *Clitoria ternatea, Phyllanthus niruri, Annona squamosa and Crateva magna* have demonstrated significant *in-vitro* and *in-vivo* antiurolithic activity. The phytochemicals such as flavonoids, alkaloids and glycosides are found to be responsible for the inhibition of calcium oxalate stones and also for the reduction of the stone's size.

Keywords: Kidney stones, urolithiasis, herbal drugs, pathogenesis

Introduction
Urolithiasis is a condition characterized by the presence of stones or calculi in the urinary system resulting from the precipitation of minerals like calcium oxalate or their salt followed by infection, obstruction, and inflammation [1]. Urolithiasis is known by other names such as renal calculi, Nephrolithiasis, or kidney stone. Urolithiasis is a term derived from Greek 'Uro' means urine 'Lith' means stone and 'iasis' means disease or condition. Kidney stone has a rich historical background. The discovery of urolithiasis dating back to around 4800 BC in Egyptian mummies underscored by Shattock's in 1905 reveals the prehistoric roots of Urolithiasis. In ancient India, Charaka and Sushruta are the two famous physicians who referenced this condition in the Hindu writings Charaka Samhita and Sushruta Samhita. The prevalence rate of urolithiasis is high in China because of their dietary habits, geographical characteristics and lifestyle. Traditional Chinese Medicines (TCM) (She wei, hai jin sha), accupuncture, and massage has been considered as a remedy of Urolithiasis. TCM are used as a remedy for kidney stone in many developing countries.

Kidney stones are of different types. They are: Calcium stones (75-85%), Struvite stones (2-13%), Uric acid stones (6-10%), Cysteine stones (1-2%) [2]. The pathology behind the condition is the imbalance between the presence of stone forming inhibitors and the promoters. The kidney stone is commonly seen in men than women between the ages of 20-40.

The rate of urolithiasis increases globally due to the multiple socioeconomic factors like dietary habits, climate, co-morbid disease and economic burden. The universal rising of urolithiasis varied across different region around the world. The 2019 Global Burden of Disease (GBD) study offers documented cases, mortality for 369 diseases and injuries occurs between 1990 and 2019 for many countries. Moreover, there were 106 million incident cases of urolithiasis in 2021, of which over 67% were in men (71.1 million) globally. 10-12% of the population in industrialized countries are affected by urolithiasis. Iran has a high prevalence rate of urolithiasis. Stone disease is uncommon in only few countries like coastal areas of Japan and Green land. Some interventional procedures such as Extracorporeal Shock Wave Lithotripsy (ESWL), Percutaneous Nephrolithotomy (PNL) or Uteroscopy (USP) are used for the treatment of stones which is larger than 5 mm or untreatable stones.

Many herbal plants and traditional plants have been utilized over several centuries. It has been proved that 80% of the world's population depends on traditional or folk medicine to cure different types of diseases [3]. They act as a credible source for drug discovery. Some medicinal plants with diuretic antioxidant and antispasmodic properties prevent crystallization, nucleation, aggregation which can be used for the treatment of Urolithiasis. The phytochemicals are the plant chemicals which are responsible for the most of the pharmacological activity of the plants. In the traditional systems of medicine, plants having these phytochemicals like quercetin, kaempferol, etc.

Were used as a remedy for urolithiasis and are proved by many other journals through systematic pharmacological and clinical studies except for some composite herbal drugs and plants. Cystone is a polyherbal formulation used for the treatment of urolithiasis which is approved by Indian regulatory authority. Cystone act as natural supplement and reference drug for the treatment of urolithiasis and for the screening of medicinal plants having antiurolithiatic potential.
There are only few studies available for the potency of antiurolithiatic activity. In the perspective of traditional use, this review article was planned to assess the potency of antiurolithiatic activity of some herbal plants.

Pathogenesis
Urinary Stone Types
Urinary stones are mainly categorized into five types:

- Calcium oxalate stones
- Calcium phosphate stones
- Uric acid stones
- Struvite stones
- Cystine stones

The most prevalent form of urinary stone is Calcium oxalate urolithiasis accounting for about 50% of all cases.[4] Hypercalciuria often associated with calcium kidney stones has an etiology that is yet to be understood. It is considered that high dietary calcium intake can promote kidney stone formation, while consuming low-calcium foods and oxalate-rich ones may decrease this risk.
Calcium phosphate stones constitute approximately 10-20% of all urinary stones. Individuals with elevated levels of phosphate in their urine (hyperphosphaturia) are more likely to have recurrence of these stones. Uric acid stones account for 10%-15% of the total urinary stones. Consistently low urine pH, hyperuricosuria, and low urinary volume are risk factors contributing to the development of these stones.
Struvite stones are also called the triple phosphate stones. The preconditions that cause the formation of these stones are urease positive urinary tract infection, hence they are also known as infection stones. Colonization of the urinary tract by urease producing bacteria like *Klebsiella, Proteus, Staphylococcus, Pseudomonas, Providentia, Serratia, and Morganella* can cause struvite stones. These occur much more commonly in females. Cystine stones, an uncommon calculus, form due to a genetic metabolic disorder called cystinuria. This disorder leads to high level concentration of cystine (oxidized form of the amino acid cysteine) in the urine, which then crystallize and form stones in the urinary tract.

Mechanism of stone formation
Super saturation of urine and the resultant crystallization are the driving force for intrarenal stone formation. Moreover the process is influenced by certain factors which are known as promoters and inhibitors [5].

Table 1: Some kidney stone promoters and inhibitors

Promoters	Inhibitors
Hypercalciuria	Citrate
Low urine pH	Phytate
Urinary tract infections	Pyrophosphate
Inherited disorders	Renal lithostathin
Sedentary lifestyle	Nephrocalcin

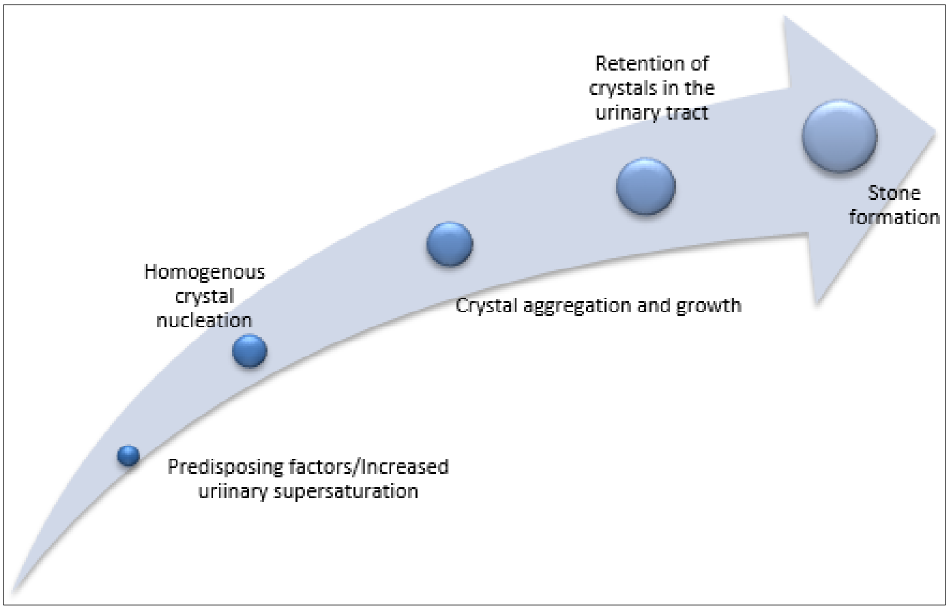


Fig 1: Mechanism of kidney stone formation

Nonetheless the type of the calculi, its formation is an elaborate and multistep process that includes urinary super saturation, crystal nucleation, growth and aggregation.
Super saturation is a state in which the presence of a solute in solution is at a concentration above its own solubility. It is the major impulse force for crystal formation.
Nucleation is the process of formation of microscopic particles due to the association of free ions in urine. Crystallization can occur in various parts of urinary tract, such as parts of nephron, surfaces of cells and on extracellular matrix. Nucleation, the event primarily involved in stone formation, may be homogeneous or heterogeneous. In an unstable solution, crystals form spontaneously by

homogeneous nucleation [6]. Much higher levels of super saturation are required to produce homogeneous nucleation than heterogeneous nucleation. Heterogeneous nucleation plays an essential role in explaining the relation between hyperuricosuria and Calcium oxalate (CaOx) stone.

Aggregation is the progression of crystals into bigger multicomponent particles. It may also happen due to the deposition of new crystals on the surface of previously formed ones. Stones can be subsequentially considered as an aggregation of crystals and a matrix that contain lipids, proteins, polysaccharides, and other cell-derived materials.

The growing CaOx crystals require plaque to anchor them and permit their development into clinically relevant stones. The Randall plaque hypothesis is quite the opposite of the above mentioned theories which suggests that the calcium deposits were mainly found on renal papillae (nearly 20%) [7]. These deposits were coined "Randall plaques" and their origin remains an issue of debate.

Plants used in the management of urolithiasis

Conventional treatment of urolithiasis shows limited effectiveness for the prevention and recurrence of stones. It is in this context that the traditionally used medicinal plants gain importance. Various herbs have been reported to be effective with lesser side effects for the treatment and this review aims to give insight about some commonly used plants in the management of urolithiasis

1. *Phyllanthus niruri L.*

Phyllanthus niruri Linn (PN) is a part of the Phyllanthus genus such as *P. abnormis, P. emblica,* and *P. fluitans,* belonging to Euphorbiaceae family, commonly referred to as "stone-breaker" due to its unique properties. The plant is wide spread across China, Malay Archipelago, India and tropical America. The medicinal potential, which includes anti-inflammatory, antiviral, antifungal, antioxidant, and anticancer properties, has been documented since the 1940s. The major phytoconstituent present in *P.niruri* is niruriside which is responsible for the antiviral activity against HIV virus.

P. niruri is a plant that is used in the traditional Brazilian medicine to treat urolithiasis. The antiurolithic activity is reported in the leaves. There are study reports which indicate that *P. niruri* can block calcium oxalate crystals and stone formation in the kidney, ureter, and urinary bladder. The efficacy of aqueous extract of *P. niruri* has been proved for inhibiting calcium oxalate crystal formation [8, 9].

2. *Annona squamosa L.*

The plant *Annona squamosa Linn* belongs to the family Annonaceae. This plant has been extensively used for various diseases. Particularly it is also known as "Sugar apple or custard apple". The plant parts like fruit, leaf, root, and even seed also have therapeutic potential. It is widely distributed in states of Andhra Pradesh, Uttar Pradesh, Madhya Pradesh, Tamil Nadu, West Bengal and Assam. Pharmacological actions such as antibacterial, antihyperlipidemic, analgesic, anti-inflammatory, antidiabetic, hepatoprotective, and antiulcer effects have been reported [10].

The findings of study titled, 'Evaluation of diuretic efficacy and antiurolithiatic potential of ethanol leaf extract of Annona squamosa Linn in experimental models', yielded promising results , demonstrating significant diuretic and antiurolithiatic activities [11]. This study provides strong evidence that the ethanol leaf extract of *A. squamosa* Linn may be a valuable therapeutic agent for the treatment of renal insufficiency and related diuretic properties and protective effects against urinary stone-induced renal damage and biochemical alterations.

3. *Gossypium herbaceum L*

Gossypium herbaceum Linn belongs to the family Malvaceae, and it is also referred to as the "cotton plant". These plants are widely distributed throughout Western India, Middle Eastern countries, Central Asia, and Africa, and graded availability is found in Iran, Russia, Afghanistan, and Turkistan. It is distributed throughout India, mainly in Andhra Pradesh, Assam, Madhya Pradesh, Punjab, and Tamil Nadu. The *G. herbaceum* is widely used in medicine as well as the production of food. The cotton seeds are excellent pain relievers and rich in vitamin E. This plant exhibits a broad spectrum of activities, including antitumor, antimutagenic, anticonvulsant, and antifungal properties as demonstrated through experimental studies. Based on literature review, the cotton seed has proved antiurolithiatic activity. The main phytochemical constituents of *G. herbaceum* include flavonoids, tannins, carbohydrates, saponins, steroids, phenols, glycosides, terpenoids, and proteins.

The antiurolithiatic activity is reported in the leaves of *G. herbaceum*. Additionally, an *in vitro* urolithiasis study was conducted on *G. herbaceum* using Neeri as a standard reference, demonstrating the plant's potential antiurolithiatic activity through significant dissolution of kidney stones [12].This study revealed that the ethanolic leaf extract of this plant exhibits higher dissolution rates than Neeri, establishing its potential as an antiurolithiatic agent.

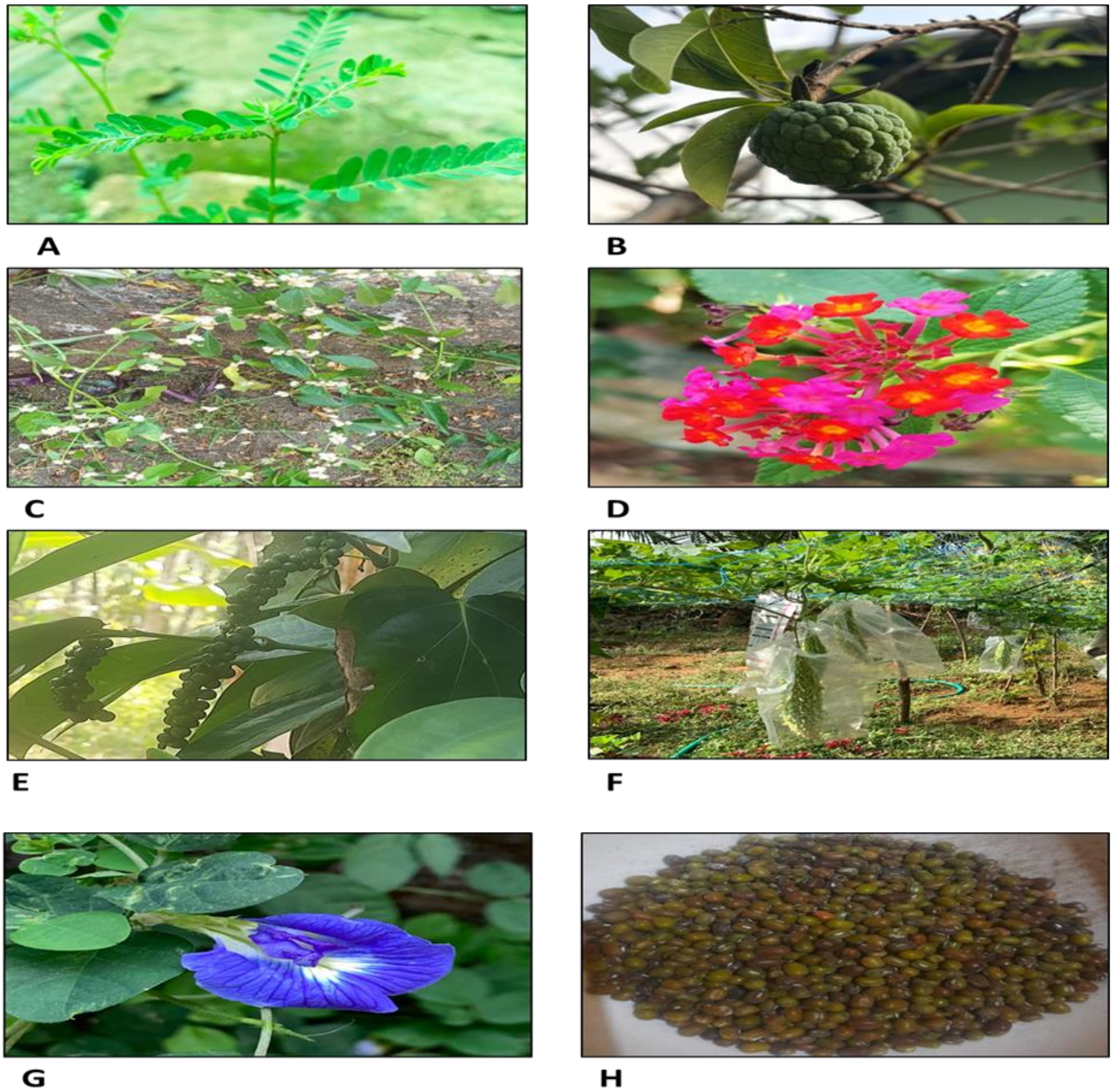
4. *Boerhavia diffusa L.*

Boerhavia diffusa (BD) Linn is a member of the Nyctaginaceae family. It is a highly valued medicinal plant in traditional Indian medicine and other global regions, including Southern America and Africa. The phytochemical and pharmacological studies have validated the traditional uses. More than 35 different types of formulations contain it as a major ingredient. Its various parts, especially roots, are used for various therapeutic purposes, such as hepatoprotective, gastrointestinal, and gynaecological indications, etc. [13]. A comprehensive review of literature reveals that *B. diffusa* possesses a diverse array of bioactive compounds, including in the root, which contains rotenoids, which are the source of isoflavanoids, flavonoids, glycosides, purine nucleosides, flavonoids, xanthones, lignans, ecdysteroids, and steroids.

Various studies have confirmed that *B.diffusa* has various activities, including hepatoprotection, immunomodulation, antifibrinolysis, antidiabetic, anti-inflammation, anticancer activity, and diuresis. The alcoholic extract of *B. diffusa root* showed activity against ethylene glycol induced urolithiasis in histopathological studies and is considered to be effective in decreasing the recurrence of renal calculi with fewer side effects [14].

5. *Bergenia ligulata*

The *Bergenia ligulata* belongs to the Saxifrage family, and it is a stone breaker. Its rhizome is the most used part for medicinal purposes. Due to its antilithic properties, it is used for the removal of kidney and urinary tract stones. They are commonly referred to as "Pashanabhed" and other names such as Asmabhedaka, Silabheda, Patharkuchi, etc. Berginin (0.9%) is the major constituent of the pashanabhed, and the other compound is in minor amounts. The phenolic compound contains (+)-afzelechin, leucocyanidin, gallic acid, tannic acid, methyl gallate, and (+)-catechin. The different chemical constituents, like coumarin, flavonoids, benzoids, and lactone, are present in the rhizomes of these plants [15]. This plant exhibits other therapeutic potential such as anti-inflammatory activity, antiviral activity, anti-bradykinin activity, diuretic activity, etc. The dried rhizome of *B. ligulata* is mainly used in traditional herbal medicine. An aqueous extract of *B. ligulata* was prepared by decoction (mother extract-35.9% w/w). The antiurolithic activity was proved by *in vitro* and *Aerva lanata* methods [16]. The *Aerva lanata* and ex vivo and real-time antiurolithiasis activity of the mother extract is described by using an aggregation assay in synthetic urine.



(A) *Phyllanthus niruri* L.(B) *Annona squamosa* L. (C) *Aerva lanata* L. (D) *Lantana camara* L. (E) *Piper nigrum* L. (F) *Momordica charantia* L. (G) *Clitoria ternatea* L.(H) *Vigna radiata* L.

Fig 2: Plants used in the management of Urolithiasis

6. *Mentha piperita L.*

Mentha piperita L. belongs to family Lamiaceae. *M. piperita* (peppermint) is regarded as one of the best potential sources of biologically active substances for the food, cosmetics, and pharmaceutical industries. This plant, native to Europe, has become naturalised globally through widespread cultivation and is occasionally found in the wild alongside its parent species all over the world. Peppermint oil contains menthol, menthyl acetate, and menthone as the main constituents. And this plant exhibits various therapeutic activities, including antiemetic, antioxidant, anti-androgenic, anti-allergic, antitumorigenic, and others [17].

Scientists studied the ability of peppermint leaf extract to prevent kidney stones. The antiurolithiatic efficacy of *M. piperita* leaf methanolic extract was evaluated by *in vitro* study [18]. The methanolic extract exhibited the most pronounced calcium oxalate dissolution, achieving a maximum efficacy of 98% and it showed better efficacy than the standard drug Neeri in calcium oxalate dissolution. This *in vitro* study reported that the methanolic extract of *Mentha piperita* shows high dissolution of calcium oxalate.

7. *Daucus carota L.*

Daucus carota Linn belongs to the family Apiaceae or Umbelliferae and is commonly used as a nutritional and medicinal plant. This is found all over the world. *Daucus carota* contains carotenoids, including alpha, beta, gamma, and zeta carotene; lycopene volatile oil, including limonene, dipentene, etc. The plant exhibits other pharmacological effects, including antioxidant activity, anticancer activity, anti-analgesic and anti-inflammatory activity, CNS activity,

antimicrobial and antifungal activities, effects on the reproductive system, cardiovascular effects, etc.
The studies were conducted on various parts of the plant and suggested that *Daucus carota* root extract possesses antiurolithiatic properties, effectively inhibiting CaOx urolithiasis *in vitro*. It exhibits significant inhibitory effects on all stages of calcium oxalate (CaOx) urolithiasis including nucleation, growth, and aggregation, while promoting the formation of more soluble calcium oxalate dehydrate (COD) crystals [19]. Further literature survey on *D. carota* insinuates that due to its widespread availability, consumption, and antilithic properties make it a promising candidate for development as an alternative or complementary treatment for CaOx urolithiasis.

8. *Aerva lanata. L*

The perennial herb mountain knotgrass, or *Aerva lanata Linn*, belongs to the Amaranthaceae family. This species has a vast geographic range and is native to Asia, Africa, and Australia. In addition to being a traditional remedy for snakebite, this plant is used as food. Significant therapeutic benefits, including antiurolithiatic, antihyperlipidemic, antibacterial, and antioxidant properties, are demonstrated by this herb. Several bioactive substances, such as proteins, carbohydrates, tannins, phenols, alkaloids, and flavonoids, are present in *A. lanata.*
The antiurolithiatic effectiveness of *A. lanata* extract and its extracted bioactive components, such as phenolics and sterols, are being assessed in current research on this plant [20]. The result of the investigations done by the analysis of urine chemistry in relation to the minerals that cause stone formation showed that, the aqueous fraction exhibited improved calcium oxalate dissolution.

9. *Chloris barbata*

Chloris barbata (syn. *Chloris inflata*), or swollen windmill grass, is a commonly seen flowering plant in the grass belongs to family Poaceae. It is used for the treatment of urolithiasis due to the presence of chemical constituents like quercetin, catechin, etc.
The geographical source of *C. barbata* was Central and South America. It plays a major role in herbal medicine and Indian culture. The plant juice is responsible for other pharmacological properties like antibacterial, anthelmintic, analgesic and antimicrobial. All parts of *C. barbata* are used for the treatment of rheumatism. The antiurolithiatic activity of ethanolic leaf extracts of *C. barbata* were evaluated by using *in vitro* antiurolithiatic model [21].

10. *Lantana camara L.*

Lantana camara Linn (commonly known as lantana) is a type of flowering plant belonging to family Verbenaceae. It is native to the American tropics and further spread into Asia and Oceania. Oleanolic acid isolated mainly from the roots of *Lantana camara* and other constituents like, flavonoids, anthocyanins, coumarins, lignans, catechins, alkaloids, and tannins are responsible for the reduction of calcium oxalate crystals.
L. camara is commonly used for pharmacological activities like antibacterial, antioxidant, antipyretic, antifungal and it is also used for the treatment of cold pox, hypertension, and bronchitis. Its essential oil called Lanthana oil is available in the market for its medical activities. The *L. camara* leaves extract proves its antiurolithiatic activity due to the suppressing activity of calcium oxalate crystal, by *in vitro* study [22].

11. *Piper nigrum L*

Piper nigrum Linn. (black pepper), known as the king of spices, is a member of the family Piperaceae that is cultivated for its fruit and dried pepper is extensively used as a condiment in Indian households. It is grown in the southern parts of India especially Kerala and other tropical locales. Fruits of *P. nigrum* have a long history in Indian traditional medicine for the treatment of gastrointestinal and respiratory ailments.
The major bioactive constituent present in *P. nigrum* is piperine. The other important phytochemicals present are amides, piperidine, pyrrolidines, and trace amounts of safrole [23]. It is commonly used to treat, malaria, skin cancer, scabies, nerve pain and other diseases. It is also proven to have, anti-pyretic, anti-apoptotic, anti-microbial, antianalgesic, anti-depressant, anti-inflammatory, anti-platelet, antifungal, immunomodulatory activity. In recent studies, the anti-urolithiatic activity piperine isolated from fruits of *P. nigrum* was evaluated by both *in vitro* and *Aerva lanata* methods [24].

12. *Momordica charantia L*

Bitter gourd (*Momordica charantia L.*) is a topical vine belonging to family Cucurbitaceae. The plant is cultivated widely in India, China, and South East Asia as vegetable as well as medicinal crop. Numerous researches have been carried out and attributed the various medicinal properties to each part of the plant, i.e., seeds, roots, leaves, and particularly the unripe fruits. The fruits and leaves contain a stearoidal saponin charantin, as its major phytoconstituent. Its fruits contain a cathartic principle called mo-mordicin, carbohydrate, mineral matter and ascorbic acid [25]. Additionally, alkaloids, glycosides, saponins and mucilage are the other contents.
Some of the important pharmacological properties include anti-diabetic, antioxidant, antidementia, and anticancer activity. In traditional system of medicine in India, the fruits of *M. charantia* are reported to be useful in the treatment of urinary stones. Scientifically both *in vitro* and *Aerva lanata* studies have demonstrated that the fruits of *M.charantia* may elicit antiurolithiatic activity [26].

13. *Crateva magna Lour*

Crateva magna Lour. Bark belonging to family Capparaceae also known as the Baruna plant is a small wild or cultivated tree found in Southeast regions of Asia especially in countries such as India, Bangladesh, China, and Malaysia. Reports demonstrate that the traditional systems of Indian medicine, such as Ayurveda and Unani utilises the pharmacological behaviour of various parts of this tree especially its bark.
The preliminary phytochemical evaluation reveals the presence of alkaloid, glycoside, phenols, flavonoid, saponin, steroid, tannin, terpenoid, sugar, and xanthoprotein. This plant is known to possess immense pharmacological activities such as antidiabetic, antipyretic, anti-inflammatory, cardioprotective, antifertility and antiurolithiatic activity. The detailed pharmacological and chemical studies on *C.magna* have been carried out by the pharmacology division of CDRI, Lucknow, India. The ethanolic extract of its bark has shown antiurolithiatic activity which is demonstrated *in vitro* in albino rats [27].

14. *Clitoria ternatea L*

Clitoria ternatea Linn is a perennial herb and is distributed mainly across the tropical regions of Asia. This species is now grown as an ornamental, fodder, or medicinal plant. A wide range of secondary metabolites, including flavones, glycosides, anthocyanins, triterpenoids, and steroids, has been isolated from *C. ternatea Linn*.

It is commonly known as "the Butterfly pea'' or Shankupushpam or Aparajitha or Asian pigeonwings. In Ayurveda, this plant is used as a laxative, memory booster, diuretic, and antihelminthic and in the treatment of infertility, dementia, burning sensation, leprosy, inflammation, leukoderma, bronchitis, asthma, pulmonary tuberculosis, ascites, and fever. The USFDA declared the additive "butterfly pea flower extract" to be exempt from certification and safe for use as colouring in alcoholic beverages, sports, and energy drinks, flavoured or carbonated water, nutritional beverages, chewing gum, teas (blue tea), ice cream and frozen dairy desserts, hard candy, and fruit preparations in yoghurts. *In vitro* antioxidant and anti-urolithiatic activities of various solvent fractions obtained from leaves of the blue-flowered variety of *C. ternatea* have been proven [28].

15. *Vigna radiata L*

The mung bean (*Vigna radiata L*.) is one of the most important edible legume crops of the family Fabaceae. It is mainly cultivated in the East, Southeast, and South Asian regions. Mung bean has an extensive history of usage as traditional medicine [29]. It has been known to be a good source of protein, minerals, dietary fibre, vitamins, and several bioactive compounds, namely polyphenols, polysaccharides, and peptides.

This plant has been shown to possess antioxidant, antimicrobial, and anti-inflammatory activities. Moreover, mung beans have antihypertensive, antidiabetic, antihypertensive, and antitumor effects, among others. The *in vitro* antiurolithiatic activity of *V. radiata* has been studied in its aqueous extract and can be considered a promising drug candidate for treating urinary stones [30].

Conclusion

This review exemplifies the potential of herbal management in the prevention and treatment of urolithiasis. Various studies suggest that herbal plants possess significant antiurolithic activity, which is attributed to the presence of various phytochemicals like flavonoids, alkaloids, and glycosides. Several herbal extracts have been shown to inhibit calcium oxalate stones and their antioxidant and anti-inflammatory properties make them potential therapeutic agents for the management of kidney stones. The use of herbal medicines for kidney stones offers many advantages, including lower costs, lower side effects, and increased accessibility. Additionally, herbal management is considered a complementary therapy to conventional treatments, enhancing their efficacy and reducing the risk of recurrence.

According to the literature survey, herbal management may be a valuable alternative to conventional treatments, offering safety, efficacy, and cost-effectiveness for the remedy of kidney stones. As the global burden of kidney stones rises, the development of novel herbal-based therapy is a much-needed solution for urolithiasis.

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