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Review

PLANT BASED APPROACHES FOR THE TREATMENT OF UROLITHIASIS

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Abstract

Medicinal plants have been known for thousands of years and are widely recognized as a valuable source of treatments for various health issues. Urolithiasis, or kidney stones, is the most common urinary disorder seen globally. Kidney stones are formed from saturated crystals made up of minerals found in urine. They mainly consist of calcium oxalate, uric acid, and phosphate crystals. While there are several synthetic medications available, traditional medicines and plants provide a promising way to treat kidney stones. Many synthetic drugs, such as diuretics and narcotic pain relievers, are used to treat kidney stones. However, the overuse of these synthetic drugs can lead to more adverse reactions. This has encouraged people to seek natural and safer remedies. This review focuses on effective local herbs used to treat urolithiasis. It aims to highlight current research trends on medicinal plants known for their activity against kidney stones. This article may assist researchers in identifying key compounds or herbal products that have urolithiatic effects.

Keywords: Medicine, Medicinal herbs, Urolithiasis, Herbal Products

Introduction:

Urolithiasis is common in the emergency department. It refers to the presence of stones in the urinary tract. Nephrolithiasis specifically means kidney stones, while ureterolithiasis refers to stones in the ureters. Urolithiasis includes all stones found in the kidneys, ureters, bladder, and urethra. This review focuses on urolithiasis. By age 70, about 11-16% of men and around 7-8% of women will have experienced symptoms related to it. Most people with urolithiasis are between 20 and 50 years old. Nearly 70% of those affected will

have recurrent stones within the next 10 years [1]. Urinary stones form from clusters of calcium oxalate in the kidneys. More men than women are affected by these stones. Patients with urinary stones excrete much higher levels of calcium and oxalate than healthy individuals. An imbalance in stone types, such as lower calcium oxalate levels, lower uric acid levels, reduced urine production, and low phosphate levels, supports the idea that these factors lead to stone formation. Lithotripsy removes stones but is often painful, making it likely for new stones to form afterward. Thus, these procedures should be avoided if possible. Phyto pharmaceutical products may help prevent urinary stones from returning. Phytotherapeutics can change how calcium and magnesium ions combine in urine. Additionally, many herbal products possess anti-lithogenic properties, especially those high in saponins. Saponins can disturb the organized structure of mucoproteins, which aids in the crystallization process [3]. Men are twice as likely to develop stones compared to women. This difference relates to lifestyle and external factors, such as diet and environmental exposure. Other influencing factors include obesity, reduced daily fluid intake, age, being Caucasian, lower socio-economic status, and certain diseases like diabetes and gout. Conditions such as Inflammatory Bowel Disease (IBD), pancreatitis, short-gut syndrome, and hyperparathyroidism can cause increased calcium levels in urine, leading to a higher chance of stone formation[2]. Although most Ayurvedic products have not been scientifically validated for specific benefits, they have served as effective treatments for renal stones for thousands of years. Many of these products help lower the risk of developing another stone without causing adverse side effects [3].

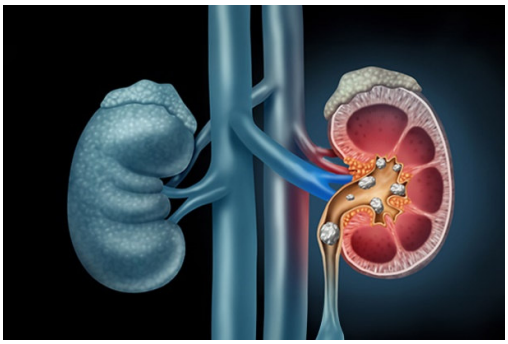

Figure: 1: Kidney stone

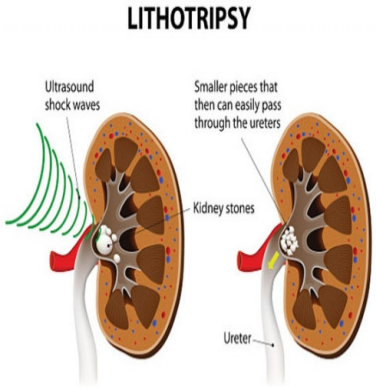

Figure: 2: Process of Lithotripsy

Etiology and pathophysiology:

Etiology:

- Having a personal and family history of kidney stones raises a patient's risk for developing more stones. Procedures like Roux-en-Y gastric bypass and sleeve gastrectomy have been linked to a three-fold increase in calcium oxalate stone formation. This happens because of the malabsorptive state following surgery, which leads to high oxalate levels, low urine production, and low citrate excretion. Certain medical

conditions, such as chronic kidney diseases, hypertension, gout, type 2 diabetes, high cholesterol, obesity, endocrine disorders, and cancers, also increase the risk of kidney stone formation. The risk for calcium oxalate and uric acid stones is particularly high with obesity, high cholesterol, and type 2 diabetes. Diets of people with high cholesterol, hypertension, and type 2 diabetes often include high levels of animal proteins, sodium, and sugar. This makes them more likely to develop kidney stones. Additionally, insulin resistance associated with obesity and type 2 diabetes raises the risks of stone formation due to high calcium and uric acid levels in the urine.

- A previous personal and family history of kidney stones significantly increases a patient's risk of forming new stones. Procedures such as Roux-en-Y gastric bypass and sleeve gastrectomy can lead to a three-fold rise in calcium oxalate stone formation due to the malabsorptive state after surgery. This condition results in higher urinary oxalate levels and reduced urine production and citrate.
- Drug-induced kidney stones are rare, accounting for only 2% of cases. Common drugs include protease inhibitors for HIV treatment, such as atazanavir and indinavir, as well as sulfadiazine. Stones from protease inhibitors are not easily seen on unenhanced CT scans and have a gelatinous composition, making them resistant to lithotripsy. They usually cause severe urinary obstruction that requires ureteral stenting. Ceftriaxone has also been linked to an increased risk of stone formation in patients undergoing long-term treatment [4].

Pathophysiology:

- Environmental and genetic factors each have a role in the complexity of urolithiasis. The process of forming urinary stones is a complex phenomenon, and the process of forming CaOx stones can be considered to be different from other types of stone formations. Ineffective renal acidification and/or increased renal excretion or increased absorption in the gastrointestinal tract of a substance can lead to the accumulation of stone-forming substances.

- Randall plaques/mineral deposits play a pivotal role among the various patho-mechanism processes for forming CaOx stones. Yet still, there is limited information regarding the development of CaOx stones and how they occur, urging further research efforts to find effective measures for prevention as well as for treatments for such conditions. Recent findings have pointed to interstitial apatite crystals as one possible initiation for developing CaOx stones.

- Decreased amounts of urine increase the concentration of substances that induce the formation of stones, and thus the phenomenon of crystallization becomes facilitated because of increased urine concentration, which remains a crucial consideration in the pathophysiology of urolithiasis. More often, kidney stones are formed in conditions of low urine production, which may occur because of dehydration, certain medications, or certain medical conditions that affect the regulation of fluids in the body. The main cause of the development of kidney stones is not drinking enough water[5].

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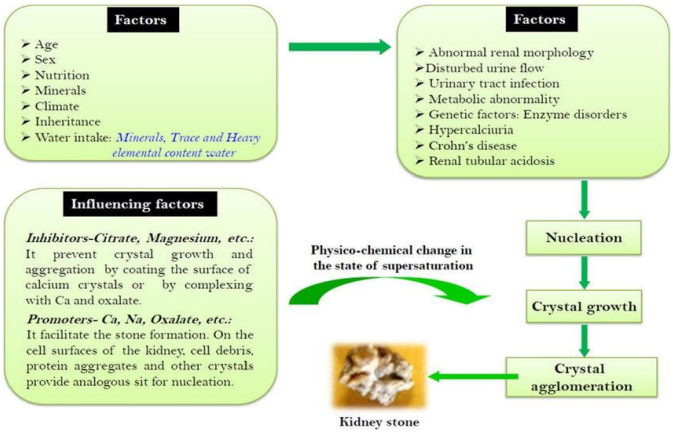

Figure: 3: Pathogenesis of Kidney Stones

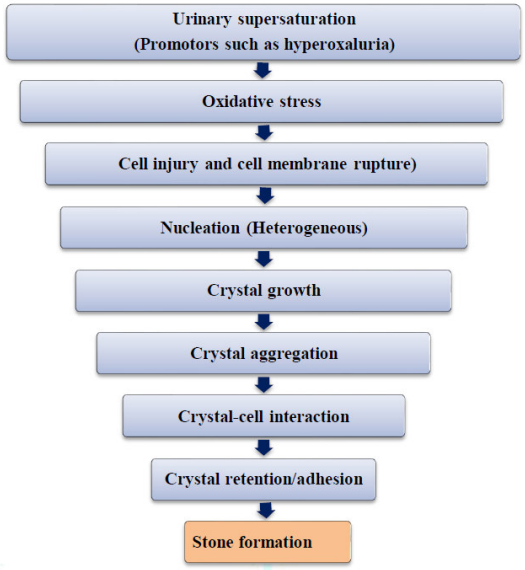

Figure: 4: Schematic representation of the various events of events of kidney stone formation

Table 1: Relationship of Stone Location to Symptoms

Stone Location	Common Symptoms
Kidney	Vague flank pain, hematuria
Proximal ureter	Renal colic, flank pain, upper abdominal pain
Middle section of ureter	Renal colic, anterior abdominal pain, flank pain
Distal ureter	Renal colic, dysuria, urinary frequency, anterior abdominal pain, flank pain

Types of Kidney Stones:

Approximately 70-80% of renal stones are made up of calcium oxalate and calcium phosphate compounds. The remaining include 10% that are struvite stones, 10% that are uric acid stones, and less than 1% that are cystine stones or drug stones, however defined. Calcium stones and uric acid stones occur mainly in males, while struvite stones are mainly found in women. Kidney stones recur in 50% of people in 10 years among those who have had a stone. The rate of recurrence in some studies among those under observation has been between 30% and 50% in 5 years. The incidence among members of the control groups in randomized trials in relation to incident cases from a first calcium oxalate stone is 2-5 per annum per year. The degree of recurrence also relates to types. Nuclear precipitation due to uric stones reduces the barring level or degree and acts to favor future precipitation in renal stones. Reduced supersaturation of the filtrate in urine reduces reformation of renal stones.

Calcium stones

The common types of kidney stones are calcium oxalate stones, which form the majority (around 80%) of stones found in kidneys. A kidney stone is a solid structure that tends to form inside a kidney in conditions where there is excess calcium, oxalate, cystine, or phosphates, as well as a low fluid volume in the kidneys. Calcium stones are normally composed of calcium oxalate in pure form, although they mostly form in a compound with calcium phosphate or calcium urate. Hypercalciuria, low urine volume, as well as a condition known as hyperoxaluria, causes the concretion to form in calcium stones. In addition, hyperalciuria can result from such diseases as hyperparathyroidism, malignancy, sarcoidosis, as well as vitamin D excess in muscles. Alkaluria is a risk factor in forming calcium phosphate stones. Hyperoxaluria is a risk factor in forming calcium stones in addition to calcium oxalate stones in conditions where there is a disease in the bowel as a result of hyperoxaluria in the

body, known as entero-hyperoxaluria, as well as genetic disorders in metabolism in the body, known as primary hyperoxaluria.

It has been suggested that dietary oxalate could play an important role in the generation of stones, and substances that contain high amounts of oxalate, such as spinach, beets, and rhubarb, would raise oxalate levels in the urine and contribute significantly to the generation of calcium oxalate stones. High doses of vitamin C might also raise the generation of oxalate because ascorbic acid is metabolized into oxalate. Less oxalate reabsorption occurs within the colon as a result of the secretion of calcium oxalate.

Volume depletion and reduced urine production are secondary to diarrheal losses. The loss of bicarbonate in the stools can result in a metabolic acidosis, leading to a reduced urinary pH and a condition of hypocitraturia because of the increased reabsorption of citrate, predisposing conducive to the formation of uric and calcium oxalate stones.

Symptom: A kidney stone may not cause symptoms until it moves around within your kidney or passes into your ureter the tube connecting the kidney and bladder. At that point, you may experience these signs and symptoms:

- Severe pain in the side and back, below the ribs
- Pain that radiates to the lower abdomen and groin
- Pain that comes in waves and fluctuates in intensity
- Pain on urination
- Pink, red or brown urine
- Cloudy or foul-smelling urine
- Nausea and vomiting
- Persistent need to urinate
- Fever and chills if an infection is present
- Urinating small amounts
- Uric acid stones

Pure uric acid stones are radiolucent on plain radiography but are visible on sonography or CT scan. Such stones often occur in patients who have hyperuricemia. Approximately 15-20% of patients with uric acid stones have had previous episodes of gout. A high-protein meat diet, which contains relatively high amounts of purine, a uric acid precursor in its breakdown, can predispose the urinary tract to the formation of uric acid stones. At a pH below 5.5, uric acid is relatively insoluble in the urinary system; however, at a pH above 6.5, its solubility increases.

Cystine stones

Cystine kidney stones result from cystinuria, an inherited (genetic) disorder of the transportation of an amino acid (building block of protein) called cystine that leads to an excess of cystine in the urine (cystinuria) with the resultant formation of cystine stones.

Cystinuria is the most common defect in the transport of an amino acid. Although cystine is not the only overly excreted amino acid in cystinuria, it is the least soluble of all naturally occurring amino acids. It has a tendency to precipitate out of urine and form stones (calculi) in the urinary tract.

Small stones are passed in the urine. However, big stones remain in the kidney (nephrolithiasis) impairing the outflow of urine while medium-size stones make their way from the kidney into the ureter and lodge there further blocking the flow of urine (urinary obstruction).

Symptoms: Cystinuria only causes symptoms if you have a stone. Kidney stones can be as small as a grain of sand. Others can become as large as a pebble or even a golf ball. Symptoms may include:

- Pain while urinating
- Blood in the urine
- Sharp pain in the side or the back (almost always on one side)
- Pain near the groin, pelvis, or abdomen
- Nausea and vomiting

Struvite stones

Struvite stones are hard mineral salts that may develop within your kidneys. Formation takes place when calcium and phosphate salts crystallize and aggregate within your kidneys. It is a type of mineral that results from bacterial activity within the urinary tract.

Approximately 10 to 15% of kidney stones are composed of struvite. However, this particular stone is found more in women than men. The struvite stone is known to develop rapidly. It may cause obstruction of the kidney, ureters, or bladder, further leading to damage to your kidney.

Symptom: Symptoms of struvite stones are similar to those of other types of stones, and can include:

- Pain in your side and back
- Fever
- Frequent need to urinate
- Pain when you urinate
- Blood in your urine [6].

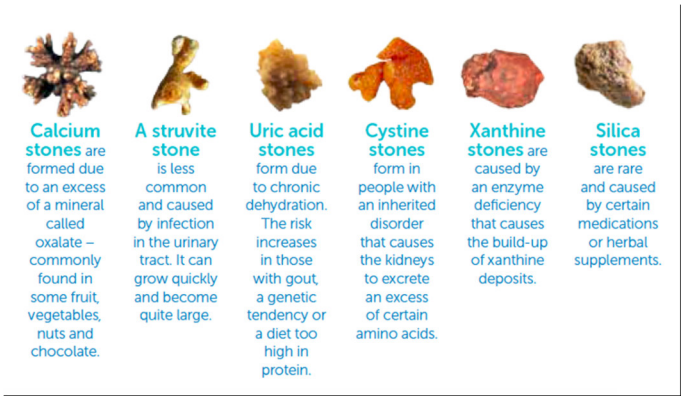

Figure: 5: Types of Kidney Stones and their Composition

Table 2: Type of stones

Type	Frequency (%)	Sex	Crystals	Radiography
Calcium oxalate/ mix	75	M	Envelope	Round, radiodense, sharply outlined
Calcium phosphate (brushite)	5	F>M	Amorphous: Alkaline urine	Small, radiodense, sharply outlined
Uric acid	5–15	M=F	Diamond; Acid urine	Round/ staghorn, radiolucent, filling defect
Struvite (Mg ammonium phosphate)	10–20	F	Coffin lid; Infection/ urea splitter	Staghorn, laminated radiodense
Cystine	1	M=F	Hexagon	Staghorn, radiodense

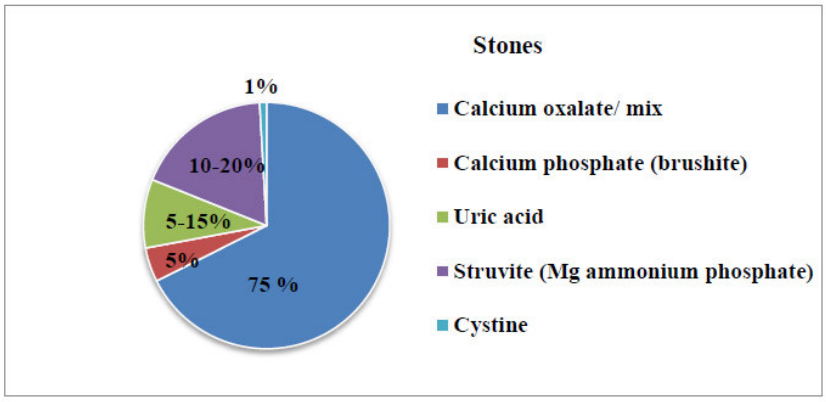

Figure: 6: Chart showing % of Stone formation

Plants sources used for Urolithiasis:

Dietary Plant-Based Practices: Whole Food and Plant-Based Diets: Emerging bodies of evidence indicate the inclusion of phytochemical-rich plant-based food products, supplements, as well as unrefined drugs in the regular diet regime of individuals. The anti-urolithiatic property of these phytochemicals in plants can be ascribed to their antioxidant, antispasmodic, diuretic, as well as inhibition in crystallization, nucleation, and aggregation properties. These modes of action can prevent the events as well as the characteristics that promote the advancement of renal calculi in individuals. It will also prevent the escalation of the secondary condition such as inflammation in addition to injury, which in most instances leads to a vicious cycle in relation to the advancement in the progression of the disease [7]. Recently, in a cross-sectional study, it was discovered that higher levels of compliance with a plant-based diet resulted in a decrease in risk factors for stone formation, although some correlations were dependent on the quality of plant products eaten[8].

Mechanisms Responsible for the Benefits of Dietary Plants: Dietary plants affect the biochemical composition of the urine in the following mechanisms:

- Alkali Load: Fruits and vegetables are known to increase the pH and citrate content of urine. These are reported inhibitors for calcium stone production [10].
- Dietary Fiber: The fiber in the diet helps in binding the oxalate and calcium in the intestinal tract, thereby preventing their absorption.
- Phytochemicals: Flavonoids and polyphenols such as catechin, quercetin, or EGCG exhibit inhibitory properties against crystallization,
- Hydration: Water-dense foods help raise fluid intake and the dilution effect of the liyhogenic substance [11].

Figure: 7: Dietary Plant-Based Food

Medicinal Plants with Antiurolithic Potential:

Several medicinal plants which are practiced traditionally around the world have been studied for their antiurolithiatic properties. The main reasons why these plants have been studied include their properties such as being a diuretic, antispasmodic, antioxidant, and crystal inhibitors [12].

There are a number of medicinal plants that have been known to be effective in the inhibition of CaOx precipitation. This study cited the works of Atmani and Khan, who showed that an extract from the plant *Herniaria hirsuta L.*, which is a lithiasis remedy in Morrocan medicine, increased the number but reduced the size of CaOx crystals. The authors showed in their subsequent study that H. hirsuta reduced the binding capacity of crystals to renal cells. Another study showed the inhibitory activity on the precipitation process of CaOx crystals using the extract from the plant *Phyllanthus niruri L.*, a urolithiasis medicine in Brazilian traditional medicine. The authors showed that the extract reduced the precipitation process of CaOx crystals. This study cited the research study on the *Vigna unguiculata* (L.) Walp. seed extract, an ayurvedic medicine in Indian traditional medicine, which showed an inhibitory activity on the precipitation process of calcium and phosphate crystals *in vitro* [9].

Figure: 8: Medicinal Plants used for Anti Urolithiatic Properties

Other Ethnomedicinal Plants:

Various ethno-botanical studies have reported the use of a number of plant species which exhibit anti-gallstone activity, especially from India, such as *Cynodon dactylon, Tamarindus indica, Ocimum sanctum,* and many others with variable experimental evidence.

Figure: 9: *Cynodon dactylon* Plant

Figure: 10: *Tamarindus indica*

***Rotula aquatica* & Traditional Ayurvedic Plants:**

Rotula aquatic Lour, an herb of immense medicinal value, is of great use in Ayurvedic medicine. It is known by another name, Pasanabheda, in Ayurvedic medicine. Several studies reported that *Rotula aquatica* possesses antiurolithiatic, hypoglycemic, anti-inflammatory, antibacterial, and anthelmintic effects. Though the information available is quite encouraging, wherein it was revealed that some of the components of this plant, such as polyphenolic and tannenic ingredients, are of prime therapeutic use [13].

Figure: 11: *Rotula aquatic* Plant

Figure: 12: Herbal Kidney Care Formulation

Phytochemicals and Mechanisms of Action: Phytochemicals present in plant extracts play a major role in the therapeutic activities of the plant extracts. Phytochemicals present in the plant extracts responsible for the management of urolithiasis include flavonoids, phenolic acids, saponins, alkaloids, and glycosides[14]. Mechanistic actions include:

- **Antioxidant Activity:** Reducing oxidative stress in renal tissues prevents damage that favors stone formation.
- **Diuretic Effect:** Increased urine output dilutes lithogenic substances.
- **Inhibition of Crystallization:** Direct interaction with crystal surfaces inhibits nucleation and aggregation.
- **Antispasmodic Action:** Soothing ureteral spasms may facilitate stone passage[15].

The phytochemicals that have been focussed upon in various studies as being potentially significant in the experimental context include catechin, epigallocatechin-3-gallate, quercetin, rutin, hyperoside and curcumin, each showing potential in experimental settings.

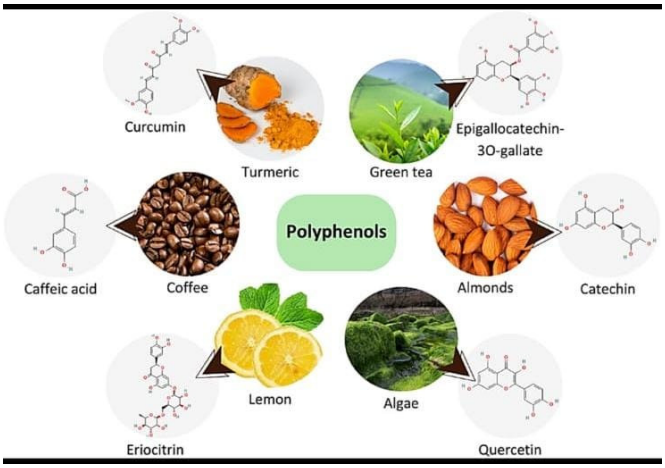

Figure: 13: Dietary Sources of Polyphenols

Preclinical Evidence:

- ***In Vitro* Studies:** Initial screening of plant extracts is done through *in vitro* assays using artificial urine and crystallization models. Most of the extracts showed significant inhibition of crystal nucleation, growth, and aggregation. These studies are very important for identifying active fractions; however, often there is a lack of translation to *in vivo* outcomes.
- **Animal Models:** Rodent models of ethylene glycol-induced hyperoxaluria remain the gold standard for preclinical evaluation. Several studies report reduced crystal deposition, normalized urinary parameters

and protection to renal histology upon treatment with extracts from Dolichos biflorus, Alhagi maurorum, and several others[11].

- Animal studies also explain mechanisms, including an increase in antioxidant enzyme activity, elevation of natural urinary inhibitors-glycosaminoglycan levels, and modification of stone-forming enzymes[16].

Clinical Evidence:

Although there is solid preclinical data, there are fewer studies on humans, and these may be limited by their small sample sizes and a lack of standardized outcomes categories [18].

- Observational and Interventional Trials: Very little information available in the literature with clinical trials indicates that a few phytomedicines may help in preventing the recurrence of stones or may stimulate the passage of the stone. For instance, Phyllanthus niruri and Hibiscus sabdariffa.
- Dietary Intervention Trials: An analysis of the role of diet, heavy in fruits and vegetables, has found a lowered risk of stones observational studies, particularly in combination with reduced sodium and controlled animal protein intake. Such intervention trials are relatively rare in the diet area also[11].
- Safety and Tolerability: Most plant extracts have been shown to be well tolerated, although it is the role of complete safety studies as well as interaction studies with conventional medications to determine this [17].
- Integration with Clinical Practice: There is a need for the integration of plant-based modalities with clinical practice for the management of urolithiasis based on clinical guidelines that make use of current evidence.

•Hydration and lifestyle change as the cornerstones of prevention.

• Plant-based diet to regulate the urinary factors.

•Use phytotherapeutic agents after considering evidence-based practice and medical follow-up.

Doctors should inform patients of both the advantages and disadvantages, including potential reactions with mainstream medicines [18].

Challenges and Future Directions:

Although there are encouraging preclinical results, there are hurdles to overcome for its implementation in the clinical setting

- Standardization of extracts, identification of bioactive compounds.
- Rigorous randomized controlled trials for the establishment of efficacy and dose.
- Post-authorization long-term safety evaluation, particularly in the presence of comorbid
- Understanding the role of food habits in addition to plant extracts[19].

The future trajectory of research should include multicenter clinical trial work, basic research at the molecular level, and combining various omics approaches to personalize plant-based medicine.

Conclusion:

Plant-based therapies, in terms of whole foods and medicinal plants, hold promise as an add-on to the management of urolithiasis. Their potential mechanisms of action could be multifactorial, including the promotion of diuresis, antioxidative properties, and the prevention of crystal formation. Although the preclinical evidence in the field has been quite strong, clinical validation of the same has become the need of the day. Evidence-based integration of these strategies may enhance patient outcomes with lower side effect profiles than conventional pharmacotherapy.

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