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A COMPREHENSIVE REVIEW ON ANTI-UROLITHIATIC HERBAL PLANTS IN THE PREVENTION AND MANAGEMENT OF KIDNEY STONES

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ABSTRACT

Urolithiasis is a common, recurrent urological condition, which is typified by the development of crystalline calculus in the urinary tract. Its rising prevalence in the world especially in third world countries and tropical areas are due to eating habits, lack of water, metabolic imbalances, and changes of lifestyles. The pathophysiology of urolithiasis is in an intricate interaction of physicochemical and biological roles, such as urine oversaturated with metallic salts, nucleation of crystals, crystal growth, aggregation and trapping at renal tubules. New data point to the important contribution of oxidative stress, inflammation and damage to renal epithelial cells in the facilitation of crystal adhesion and stone formation. Medical methods like pharmacotherapy and surgery used in the conventional treatment are effective in removal of stones, but they are mainly linked with high recurrence rates, adverse side effects and high cost. It is in this regard that medicinal plants have received a lot of focus as alternative and complementary therapeutic agents because of their safety, affordability, and multi-targeted action. A number of plants, such as *Bryophyllum pinnatum*, *Zea mays*, *Piper betle*, *Didymocarpus pedicellatus*, *Tribulus terrestris*, *Boerhaavia diffusa*, and *Phyllanthus niruri*, have shown pronounced antiurolithiatic activity due to their ability to inhibit crystal nucleation, crystal growth and aggregation, diuretic action, antioxidant activity, and nephroprotection. This is a review of the pathophysiology of urolithiasis and a critical analysis of therapeutic promise of medicinal plants with a special focal on their phytochemical constituents and actions. The results indicate that plant-based treatments provide good alternatives in prevention and treatment of kidney stones which have promising potential, are cost-effective and safer. Nevertheless, additional clinical trials and standardization are needed to prove their effectiveness and enable the introduction of them into the contemporary medical systems.

INTRODUCTION

Kidney stone disease, also known as urolithiasis, is a common and recurrent urological illness that poses a serious health issue in the whole world. Urolithiasis has become very common especially in the last few decades, especially in the third world like India, and in areas with hot climates like Southeast Asia and the Middle East [1,2]. It is also approximated that the rate of prevalence in almost 10-15 percent of the entire world population is at some point in life and a greater prevalence is recorded in the males and a high probability of relapse [3].

Urolithiasis is described as the presence of crystalline calculi in the urinary tract as a result of oversaturation of the urine with lithogenic substances like calcium, oxalate, phosphate and uric acid. The stone pathogenesis is a complex process, which entails nucleation, crystal growth, aggregation and retention in the renal tubules [3,4]. The condition presents clinically as acute renal colic, hematuria, nausea, vomiting, with a few cases being urinary obstruction and infection. Interestingly, the recurrence rates are high and about 50 percent of patients relapse after about 5-10 years [2].

Various risk factors lead to the occurrence of urolithiasis among them being improper intake of fluids, excessive intake of animal proteins and diets rich in oxalates, obesity, metabolic disorders, hypercalciuria and hyperoxaluria, and intestinal infections [1,3]. Besides these, it has been recently shown that oxidative stress and renal epithelial injury are the most essential factors that contribute to crystal adhesion and retention thus supporting stone formation [5]. Such results show that not only physicochemical processes are involved in urolithiasis but also intricate molecular and cellular processes.

The pharmacological therapy, changes in diet and lifestyle, and surgical treatment, which may be extracorporeal shock wave lithotripsy, ureteroscopy, and percutaneous nephrolithotomy, are the current approaches to urolithiasis management. In spite of the effectiveness of these methods in stone removal, they are usually linked to limitations which include being expensive, having side effects, failure to remove all the stones and being frequently recurrent [2,6]. All these issues highlight why alternative and more sustainable methods of therapy need to be offered.

Medicinal plants have over the past few years been drawn to increased interest as alternative or complementary therapy in the prevention and management of kidney stones. Herbal medications have long been used over the centuries and are seeing more scientific backing that proves their effectiveness and safety [7]. The mechanisms of action of these types of plant therapies include inhibition of crystal nucleation, growth, and aggregation; diuretic effects to increase stone elimination; anti-oxidant effects to reduce oxidative stress; and anti-inflammatory and nephroprotective effects to prevent the damage of renal tissues [5,8].Hence, the current review will give an overall picture of the pathophysiology of urolithiasis as well as critically assess the anti-urolithiatic effects of some medicinal plants of interest. Their phytochemical constituents, mechanisms of action, and pharmacological activities are given prominence with the aim of focusing on their potential in coming up with safer, effective and economically viable therapeutic options to kidney stones management.

Pathophysiology of Urolithiasis

The pathophysiology of the kidney stones is a multifactorial process, which takes place as a result of the oversaturation of urine with the lithogenic salts, i.e., calcium, oxalate, phosphate, magnesium, and uric acid. In case the concentration of these solutes is higher than their solubility, they precipitate and cause the formation of crystals in the urinary tract [9]. Urinary pH, ionic strength, urine volume, and relative amounts of crystallization promoters and inhibitors are the factors affecting this process. Besides physicochemical determinants, biological processes including oxidative stress, epithelial damage to kidney and inflammation are equally essential in the formation of stones. Reactive oxygen species (ROS) cause damage of the renal tubers cells, leading to crystal sticking and trapping in the kidney [10]. Additionally, other macromolecules, including Tamm-Horsfall protein, osteopontin and glycosaminoglycans, control the crystal formation by either promoting or inhibiting aggregation [11].The crystallization that takes

place and results in the formation of urinary stones is done in three broad steps, which include: nucleation, crystal growth and aggregation.

Nucleation

The first and most important process in the formation of stones is the nucleation process, which involves the mixing of the dissolved ions in the supersaturated urine to form minute crystal nuclei. It may happen through homogeneous nucleation (spontaneous nucleation in solution) or heterogeneous nucleation when crystal grows on already formed surfaces, i.e. renal epithelial cells, cellular debris, or Randall plaques [12].The major driving force in nucleation is supersaturation and the urinary pH, temperature and the ionic concentration play a significant role in this phase. As an example, acidic urine is more favorable in the formation of uric acid stones, with alkaline urine being more favorable in the formation of calcium phosphate.

Crystal Growth

Once the nucleation process is complete, the formation of the crystal takes place by a process of constant deposition of the ions of the supersaturated urine on the crystal surface. It is dependent on the extent and duration of supersaturation, urinary stasis and accessibility of binding sites [9]. Some urinary substances inhibit crystal growth such as citrate, magnesium and nephrocalcin which combines the crystal surfaces and prevents additional deposition. On the contrary, the high contents of calcium and oxalate stimulate crystalline enlargement. Recurrent development results in the development of clinically significant calculi.

Aggregation

Aggregation entails the combination of the single crystals into large particles by the process through which the crystals stick together. This is necessary to form large stones that could result in obstruction and clinical symptoms. The urinary macromolecules, ionic strength, and hydrodynamic conditions in the renal tubules affect crystal aggregation [11]. Slow or urinary stasis increases the chances of aggregation by prolonging the amount of time the crystals are in contact with one another. There is also evidence to show that, broken renal epithelial surfaces also contribute to the adherence of crystals, which further encourages the formation of stones.

Role of Oxidative Stress and Inflammation

Recently, the importance of oxidative stress and inflammation in urolithiasis has been highlighted. ROS also cause lipid peroxidation and cellular damage in tubular epithelium of the kidney, which provide sites of crystal attachment [10]. Inflammatory mediators such as TNF-α, IL-6, and monocyte chemoattractant protein-1 (MCP-1) further exacerbate renal damage and promote crystal retention [13].

Role of Inhibitors and Promoters

The balance between crystallization inhibitors and promoters is crucial in determining stone formation:

- Inhibitors: Citrate, magnesium, pyrophosphate, glycosaminoglycans
- Promoters: Calcium, oxalate, uric acid, low urine volume

A deficiency of natural inhibitors or an excess of promoters leads to an increased risk of stone formation.

Table 1: Table: Key Stages in the Pathophysiology of Kidney Stone Formation

Stage	Description	Key Factors Involved	Clinical Significance
Nucleation	Formation of initial crystal nuclei from supersaturated urine	Supersaturation, pH, ionic strength, Randall's plaques	Initiates stone formation
Crystal Growth	Enlargement of crystals by deposition of ions	Calcium, oxalate concentration, duration of supersaturation	Leads to increase in crystal size
Aggregation	Clumping of crystals into larger masses	Urine flow, macromolecules, epithelial injury	Formation of clinically detectable stones
Retention*(added for impact)*	Adhesion of crystals to renal epithelium	Oxidative stress, inflammation, cellular damage	Critical for persistent stone development

3. Types of Kidney Stones

Calcium Stones

The most prevalent type of kidney stones constitutes almost 70-80 percent of all types of kidney stones, which are calcium stones. These are mostly in form of calcium oxalate stones and rarely in form of calcium phosphate like brushite or hydroxyapatite. Calcium oxalate

stones formation is closely linked to hyperoxaluria, hypercalciuria, low urinary citrate levels, and dehydration which combined with each other facilitate supersaturation and crystallization. Calcium phosphate stones, however, are usually associated with a high urinary pH and metabolic diseases like renal tubular acidosis. This is due to the fact that promoters (calcium and oxalate) and inhibitors (citrate and magnesium) are imbalanced and that their presence in the renal tubules causes nucleation, crystal growth, and aggregation of the crystals [14].

Struvite Stones

Infection stones or Struvite stones, are magnesium ammonium phosphate stones that are highly correlated with urinary tract infection caused by urine-producing bacteria like Proteus, Klebsiella and Pseudomonas. These microorganisms generate urease that decomposes the urea to ammonia and thus urinary pH rises and causes the formation of struvite crystals. These are stones which grow very fast and are prone to developing large staghorn calculi which may occupy the renal pelvis and the calyces. Struvite stones are not usually detected early because of their predisposition to urinary tract infections and unlike in men they are more prone to occur without the early symptomatic signs [15].

Uric Acid Stones

Uric acid stones are a type of kidney stones that is formed by a large concentration of uric acid in the urine and are estimated at 5-10 percent of all kidney stones. They are usually linked to gout, metabolic syndrome, obesity and type 2 diabetes mellitus. The persistently acidic urine (pH below 5.5), decreasing the solubility of uric acid and favouring crystallization is also a major consideration in their formation. Their development is mostly due to dietary habits especially large consumption of purine-rich foods including red meat, organ meats as well as seafood. In contrast to calcium stones, uric acid stones are radiolucent and they may not be easily identified by the use of conventional radiographic techniques making the use of advanced imaging techniques to accurately diagnose them a necessity [16].

Cystine Stones

Cystine stones are infrequent and arise due to a genetic disease called cystinuria that is the failure of the renal tubular reabsorption of cystine and other dibasic amino acids. This causes excessive urine loss of cystine which is a low solubility amino acid that causes the formation of crystals and consequently the formation of stones. These are stones that are commonly found in younger people and are described by high recurrence rate as they are hereditary. Cystine stones are prone to not responding to the common methods of treatment and they demand a long term management practices such as high fluid intake and urinary alkalinization to prevent recurrence and stone formation [17,18].

Medicinal Plants Used in the Management of Urolithiasis

Panfuti (*Bryophyllum pinnatum* / *Kalanchoe pinnata*)

Bryophyllum pinnatum (synKalanchoe pinnata), is the commonly used Pafuyti, or Panfuti, in the traditional medicine of the treatment of kidney stones. The plant also has high antiurolithiatic, diuretic and nephroprotective effects. Its therapeutic effect is primarily explained by such bioactive components as flavonoids, triterpenoids, and phenolics. These phytochemicals assist in lowering urinary super saturation, stopping crystal aggregation and formation and enhancing dissolution of calcium oxalate crystals. Experiments have shown that B. pinnatum extracts have the ability to lower the crystal deposition in renal tissues and enhance renal performance by lowering oxidative stress and inflammation. Moreover, it has diuretics effect, and thus aids in flushing small calculi in urinary tract [19, 20].

Fig. 1.*Bryophallum pinnatum*

Maize Silk (*Stigma maydis / Zea mays* L.)
Maize silk is one of the commonly used herbal remedies to treat urinary problems, including urolithiasis, since it is the dried stigma of *Zea mays* L. It has diuretic, anti-inflammatory, and antioxidant effect, and this is what adds to its antiurolithiatic effects. Flavonoids, saponins and potassium salts increase the volume of urine and prevent the increase in concentration of lithogenic elements in urine. Maize silk is also useful in offering urinary PH balance and alleviating irritation of the urinary tract. Research indicates that it has the ability to prevent calcium oxalate crystal formation and lessen oxidative stress on renal epithelial cells, thereby preventing the development and progression of stones [21].

Fig.2 *Zea mays*

Tagetes erecta L.
Tagetes erecta (marigold) has long been used, in a number of medicinal uses such as kidney stones. The bioactive compounds in the plant include flavonoids, carotenoids and essential oils that are antioxidants and anti-inflammatory compounds. The compounds are used to mitigate the renal damage caused by oxidative stress and prevent the formation of crystals. There are also indications of mild diuretic properties of the plant that helps in the excretion of urinary calculi. Despite a lack of research, preliminarily, it has been shown that it could act as a prevention of the formation of calcium oxalate crystals and the preservation of renal tissues [22].

Fig.3.*Tagetes erecta*

Betel Leaf (*Piper betle*)
Piper betle widely referred to as betel leaf is one of the traditional medicines that is highly used in the traditional medicine systems due to its antioxidant, antimicrobial, and anti-inflammatory effects. When applied to urolithiasis disease, P. betle demonstrated possible antiurolithiatic properties and thus crystal nucleation and aggregation were inhibited. Its anti-oxidant effect with phenolic compounds like chavicol and eugenol helps in its anti-oxidant protective effect on renal epithelial cells. Also, it has a mild diuretic action, which strengthens the urinary flow, thus promoting the removal of small stones and its inability to be deposited [23].

Fig. 4. *Piper betle*

Didymocarpus pedicellatus
Didymocarpus pedicellatus is a medicinal plant that plays a very significant role in Ayurvedic medicines like Cystone, which is used to treat kidney stones. It has strong antiurolithiatic, lithotryptic and nephroprotective effects. The plant aids in the dissolution of calculi, decrease of crystal formation and relapse. Its action mechanism includes inhibition of calcium oxalate crystal formation, relaxation of the urinary tract smooth muscles and

decreased inflammation. Its efficacy in decreasing the size of the stones and enhancing the urinary parameters has been supported by clinical and experimental research in patients with urolithiasis [24].

Fig. 5.*Didymocarpus pedicellatus*

Tribulus terrestris

One of the commonly used medicinal plants in the traditional systems of medicine is *Tribulus terrestris* which is known to be useful in treating urinary pathology such as urolithiasis. It has high diuretic, lithotripic and antiurolithiatic effects. Saponins (especially protodioscin), flavonoids, and alkaloids are the bioactive compounds found in the plant and help in its therapeutic properties. Its diuretic effect stimulates urine flow, thus decreasing the concentration of building block and promoting the removal of little stones. Also T. terrestris was proved to suppress calcium oxalate crystal deposition of renal tissues, as well as decreased oxidative stress and so, inhibited damage of the renal epithelia. Lithotripic action of the plant helps to dissolve bigger stones into smaller pieces, which will be easy to excrete via the urinary tract [25].

Fig. 6. *Tribulus terrestris*

Boerhaavia diffusa

Punarnava *Boerhaavia diffusa* is widely used in Ayurvedic medicine as an anti-inflammatory, nephroprotective, and diuretic. Bioactive compounds found in this plant include alkaloids (punarnavine), flavonoids, and lignans, which add to the pharmaceutical effects of the plant. It aids in the prevention of the development of renal stones by minimizing the urinary oversaturation of calcium and oxalate and the aggregation of crystals. In addition, it has antioxidant capacity that prevents oxidative damage in the renal tubular cells, and anti-inflammatory properties that minimize the damage of the renal tissue. The diuretic effect increases the amount of urine which removes small crystals thus avoiding their retention in the kidneys [26].

Fig.7. *Boerhaavia diffusa*

Phyllanthus niruri

One of the best-researched plants in treating urolithiasis is the *Phyllanthus niruri* that is also known as the stone breaker. It shows strong antiurolithiastic, anti-oxidant, and anti-spasmodic effects. Phyllanthin, hypophyllanthin, and tannins are lignans, flavonoids and tannins that are present in the plant and that are important in preventing the nucleation, growth and aggregation of calcium oxalate crystals. Also, P. niruri decreases the attachment of the crystals to the renal epithelial cells and facilitates their elimination by sphincteric relaxation of the urinary tract smooth muscles. It also aids in the normalization of the urinary composition by increasing the amount of citrate and decreasing the amount of oxalate excretion and thus a major decrease in the potential risk of stone formation and recurrence [27,28].

Fig.8. *Phyllanthus niruri*

Aerva lanata

Aerva lanata is a commonly used traditional medicine in curing kidney stones and urinary disorders. It has diuretic, anti-inflammatory and anti-crystallization action. The alkaloids, flavonoid and saponins found in the plant are useful in decreasing the supersaturation of stone forming constituents in urine. It also prevents the growth and deposition of calcium oxalate crystals and increases their dissolution. A. lanata works as a diuretic that improves urine flow, which gets rid of tiny stones and does not accumulate in the urinary system. It is also an antioxidant and protects the renal tissues against the oxidative stress damage [29].

Fig.9. *Aerva lanata*

Table 2: Medicinal Plants Used in the Management of Urolithiasis [30]

Plant Name	Active Constituents	Mechanism of Action	Study Type
Bryophyllum pinnatum (*Kalanchoe pinnata*)	Flavonoids, triterpenoids, phenolic compounds	Inhibits crystal nucleation and aggregation, antioxidant, diuretic, reduces calcium oxalate deposition	*In vivo*, *In vitro*
Zea mays (Maize silk)	Flavonoids, saponins, potassium salts	Diuretic, reduces urinary supersaturation, anti-inflammatory, inhibits crystal formation	*In vivo*
Tagetes erecta	Flavonoids, carotenoids, essential oils	Antioxidant, reduces oxidative stress, inhibits crystal aggregation	*In vitro*, *In vivo*
Piper betle	Phenolics (chavicol, eugenol), flavonoids	Antioxidant, anti-inflammatory, inhibits crystal nucleation and adhesion	*In vitro*
Didymocarpus pedicellatus	Alkaloids, glycosides, flavonoids	Lithotriptic, reduces stone size, inhibits calcium oxalate crystallization	*In vivo*, Clinical
Tribulus terrestris	Saponins (protodioscin), flavonoids	Diuretic, lithotriptic, reduces calcium oxalate deposition, antioxidant	*In vivo*
Boerhaavia diffusa	Alkaloids (punarnavine), flavonoids, lignans	Nephroprotective, diuretic, reduces crystal formation, anti-inflammatory	*In vivo*
Phyllanthus niruri	Lignans (phyllanthin), flavonoids, tannins	Inhibits crystal growth and aggregation, reduces adhesion, antispasmodic	*In vitro*, *In vivo*, Clinical
Crataeva nurvala	Triterpenoids, flavonoids, saponins	Improves bladder tone, reduces urinary retention, prevents crystal accumulation	*In vivo*
Bergenia ligulata	Bergenin, flavonoids, tannins	Lithotriptic, dissolves stones, inhibits calcium oxalate crystallization	*In vitro*, *In vivo*
Herniaria hirsuta	Saponins, flavonoids, coumarins	Prevents crystal adhesion, promotes excretion, diuretic	*In vitro*, *In vivo*
Aerva lanata	Alkaloids, flavonoids, saponins	Diuretic, anti-crystallization, reduces supersaturation, antioxidant	*In vivo*

CONCLUSION

Urolithiasis has been ranked as a major health issue in the world because it is very prevalent, recurrent and has morbidity. The pathophysiological process of the disease is complex with urinary supersaturation, crystals nucleation, growth, aggregation, and retention, and contributory factors of oxidative stress, and

inflammation. Even though the traditional therapy methods like the use of pharmacological agents and surgical procedures are effective in removing stones, they, in most cases, are restricted with high rates of recurrence, side effects and economic status.

Medicinal plants have proved to be potential alternatives or complements in the treatment of kidney stones in the recent past. The current review has pointed out several plants such as *Bryophyllum pinnatum*, *Zea mays*, *Tagetes erecta*, *Piper betle*, *Didymocarpus pedicellatus*, *Tribulus terrestris*, *Boerhaavia diffusa*, *Phyllanthus niruri*, *Crataeva nurvala*, *Bergenia ligulata*, *Herniaria hirsuta* and *Aerva lanata* to have great antiurolithiatic activity. These plants work by several means like crystal formation and aggregation inhibition, urinary output increase, antioxidant and anti-inflammatory, and renal tissue protection.

Phytotherapy should be incorporated in the management of urolithiasis as a multi-targeted intervention that is cost-effective and has few side effects. Nevertheless, even with the positive preclinical and small clinical data, clinical trials, standardizing of herbal preparations, and pharmacokinetic and toxicity research are required to determine the therapeutic efficacy and safety of herbal preparations. Further studies on the discovery of active constituents and their mechanism of action will be more helpful in creating new plant-based antiurolithiatic agents. The medicinal plants have a great potential as effective and safer treatment methods of preventing and controlling urolithiasis and can be incorporated in modern evidence-based healthcare practices.

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