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Herbal Resources with Antiurolithiatic Effects: A Review

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ABSTRACT: Urolithiasis defined as the urinary stone originating anywhere in the urinary tract. Medicinal plants are established as renewable sources with antiurolithiatic effects. There are many marketed formulations which are having antiurolithiatic activity, some of them are Cystone, Calcuri and Chandraprabha bati. These formulation have been widely used clinically to dissolve urinary calculi in the kidney and urinary bladder. Apart from these, there are series of other traditional plants available and have been scientifically assessed for their antiurolithiatic activity. So the present review article explain the potential of medicinal plants in the treatment of urinary stone.

KEYWORDS: Medicinal Plants; Urolithiasis; Antiurolithiatic Activity; Hyperoxaluria.

INTRODUCTION

Urinary stone occupy an important place in everyday urological practice. The average life time risk of stone formation has been reported in the range of 5-10 % in which there is a predominance of men over women that can be observed with an incidence peak between the fourth and fifth decade of life. Reoccurrence of stone formation is a common part of the medical care of patients with stone disease[1]. These stones may be classified on the basis of their constituent i.e. Calcium-containing stones, specially calcium oxalate monohydrate, calcium oxalate dihydrate and basic calcium phosphate are the most commonly occurring ones to an extent of 75-90% , magnesium ammonium phosphate (Struvite) to an extent of 10-15%, uric acid 3-10% and cystine 0.5-1% . Out of all the types most common type is calcium oxalate or magnesium ammonium phosphate type which generally occurs commonly[2][3].Many medications and remedies have been used during the past many years to treat urinary stones. Generally in the traditional systems of medicine, the majority of the remedies are based on plants and they were proved to be useful though the rationale behind their use is not well established through systematic pharmacological and clinical studies except for some composite herbal drugs and plants. Pharmacotherapy can reduce the recurrence rate. The use of plant products with claimed uses in the traditional systems of medicine assumes importance.

In the Ayurvedic system of medicine in india, plants which belongs to 'Pashanabheda' group are claimed to be useful in the treatment of urinary stones. 'Pashanabheda' is the Sanskrit term used for a group of plants with diuretic and antiurolithiatic activities[4] [5].

Drugs with multiple mechanisms of protective action may be one way forward in minimizing tissue injury in human disease[6]. Herbal medicines contain several phytoconstituent and exert their beneficial effects by multiple mechanisms like:

- By increasing the urine volume, pH and anti-calcifying activity (Diuretic activity) helps in spontaneous passage.
- By balancing the process of Inhibition and promotion of the crystallization in urine it affects the crystal nucleation, aggregation and growth (Crystallization inhibition activity)
- Relieves the binding mucin of calculi (lithotriptic activity)
- By Improving renal function
- Regulation of oxalate metabolism
- Regulates the crystalloid colloid imbalance and improve renal function, thus prevents recurrence of urinary calculi.
- Improve renal tissue antioxidant status and cell membrane integrity and prevent reoccurrence (Antioxidant activity)
- ACE and Phospholipase A2 Inhibition
- Exerts significant anti-infective action in against the major causative organisms (Antimicrobial activity)
- Reveals marked improvement in symptoms of urinary calculi like pain, burning micturition and haematuria (Analgesic and anti-inflammatory activity).

Triterpenes having Antiurolithiatic Activity:

Naturally occurring pentacyclic triterpenes of plant origin have been identified as possessing a wide range of pharmacological effects. In animals Lupeol is found to be efficient in reducing the risk of stone formation by way of preventing crystal-induced tissue damage and dilution of urinary stone-forming constituents. Two structurally related triterpenes, lupeol and betulin were assessed for their antilithiatic effect. Foreign body implantation method followed by supplementation of ammonium oxalate was adapted to induce stone formation in the bladder. This led to elevated lipid peroxidation and depleted antioxidant status in the renal tissues. Both the triterpenes were equally efficient in minimizing crystal-induced renal peroxidative changes measured in terms of malondialdehyde and subsequent tissue damage. The antioxidant status, comprising of the enzymatic and non-enzymatic components, was found to be significantly depleted in the kidney and bladder of stone-forming animals. Both lupeol and betulin were comparable in their ability to restore the thiol status and the antioxidant enzymes like superoxide dismutase, catalase and glutathione peroxidase. The mechanism by which the two compounds render protection against oxalate-induced toxic manifestations and free radical production may involve the inhibition of calcium oxalate crystal aggregation and enhancement of the body defence systems[7].

Marketed Herbal Formulations having Antiurolithiatic Activity:

There are many marketed formulations which are having antiurolithiatic activity, some of them are Cystone (Himalaya Drug Company, India), Calcuri (Charak Pharmaceuticals, Bombay, India) and Chandraprabha bati (Baidyanath, India). These formulation have been widely used clinically to dissolve urinary calculi in the kidney and urinary bladder. Pharmacological and clinical studies carried out on a composite herbal formulation, Trinapanchamool consisting of five herbal drugs namely *Desmostachya bipinnata*, *Saccharum officinarum*, *Saccharum nunja*, *Saccharum spontaneum* and *Imperata cylindrica* was found to be effective both as prophylactic in preventing the formation and as curative in dissolving the pre-formed stones in albino rats. The antiurolithiatic activity of this formulation has been attributed to its diuretic activity[8].

CLINICAL & PHARMACOLOGICAL STUDIES:

In recent few years, a number of proprietary compositae herbal drugs have also been introduced for dissolving kidney calculi of which mention may be made Cystone [9] (Himalaya Drug Co. Bombay) and Calcuri (Charak Pharmaceuticals Bombay). These drugs are common use in India. Saxifraga ligueata and Tribulus terrestris are the two common plant ingredients of both these herbo-mineral preparation. Uretreic calculus disappeared within 55 days of treatment with 'Cystone' a herbo-mineral composition[10] [11]. Cystone works by relaxing the detrusor muscles and increasing the diuresis by

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virtue of its high content of natural mineral salts. Cystone has also been found to be useful in urolithiasis, crystalluria and urinary tract infection[12] .Pharmacologically, *Berginia ligulata* shows no effect in preventing the stone formation but it is useful in dissolving zinc calculi in the urinary bladder[13] . Varuna, Ghokhru and Kulatha also found to be effective in preventing the deposition of the stones. Vataj (oxalate) and Pitiaj (urate and cystine) stones did not dissolve in varuva and kulatha. Gokhru decoctions dissolve urate and cystine stones to some extent.

Kaphaj (phosphetic) stones were dissolving in all the three drugs. Among them kulatha had marked (87 %) dissolving activity and stones become friable[14]. There are many herbal preparations described in Ayurvedic a text in which kulatha is the main ingredient. It has been described as Ashmarighana (Destroyer of stone) by Charak, Sushruta and Other authorities. Sushruta mentions its efficacy in vataj ashmari with the characteristics of oxalate stone. Clinical investigations have been shown that out of fifteen cases urinary calculi, nine patients passed their stones within 8-10 days of treatment with *Dolichos biflorus*. Spontaneous passage of stones was common depending upon the size, site and mobility of the calculus[15] [16].

Regulates the Crystalloid Colloid Imbalance and Improve Renal Function:

In urine there are a number of crystalloids present which are of different types (oxalate, uric acid, calcium, cystine) which are kept in solution by the presence of colloids (mucin and sulphuric acid) in the urine by the process of absorption.

Table. List of some plants which have been used for the treatment of urolithiasis

Phytotherapeutic agent	**Type of study**	**Mechanism of action**
Herniaria hirsute	*in vitro*, cell culture, *in vivo*	Decrease crystal size & increase COD, diuretic
Amni visnaga	*in vivo* animals, cell culture	Potent diuretic, khellin & visnagin prevent renal epithelial cell damage caused by oxalate & COM
Tribulus terrestris	*in vitro*, cell culture, *in vivo* animals	COM, Decreases oxalate
Bergenia ligulata	*In vitro, in vivo* animals	COM, Decreases calcium
Dolichos biflorus	*In vitro*	oxalate crystals
Aerva lanata	*In vivo* animals	Decrease crystal ppt
Vediuppu chunnam	*In vivo* animals	Decrease urinary calcium oxalate, uric acid & Diuretic
Raphanus sativus	*In vivo* animals	Diuretic
Achyranthus Aspera	*In vitro*, cell culture, animals *in vivo*	Prevent renal epithelial damage, Diuretic
Quercus salicina	cell culture	Reduction in oxalate induced renal epithelial cell injury
Phyllanthus niruri	*In vitro, in vivo* animals	Antispasmodic & relaxant
Cranberry juice	Humans *in vivo*	Decrease urinary oxalates
Cynodon dactylon	*In vivo* animals	Increase COD as compare to COM

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Grapefruit juice	Humans *in vivo*	Increases urinary excretion
Paronychia argentea	*In vivo* animals	Antioxidant activity
Lemonade juice	Humans *in vivo*	Increases urinary excretion
Moringa oliefera	*In vivo* animals	Diuretic, improved renal function

When there is imbalance in the crystalloid-colloid ratio, i.e., increase in crystalloid and fall in colloid level leading to formation of renal stones or when the colloid lose the solvent action or adhesive property, urinary stones are formed[17]. Increased urinary phosphorus excretion along with oxalate stress seems to provide an environment appropriate for stone formation by forming calcium phosphate crystals, which epitaxially induces calcium oxalate deposition. Uric acid interferes with calcium oxalate solubility and it binds and reduces the inhibitory activity of GAGS. The predominance of uric acid crystals in calcium oxalate stones and the observation that uric acid binding proteins are capable of binding to calcium oxalate and modulate its crystallization also suggests its primary role in stone. formation. Supersaturation of these urinary colloids results in precipitation as crystal initiation particle which when trapped acts as a nidus leading to subsequent crystal growth. *Rubia cordifolia, Aerva lanata, Moringa oleifera* and Cystone (polyherbal formulation) maintain crystalloid-colloid balance by decreasing excretion of urinary calcium, oxalate, uric acid, phosphorus and protein in urolithiasis[18].

Improved Renal Function:

In urolithiasis, the Glomerular Filtration Rate (GFR) decreases due to the obstruction to the outflow of urine by stones in urinary system, due to this the waste products, particularly nitrogenous substances such as urea, creatinine and uric acid get accumulated in blood[19]. Herbal therapy improves the renal function by increasing the excretion of urea and creatinine. Most of the phytothereupatic agent exerts their antiurolithiatic effect through this mechanism. *Moringa oleifera* and *Rubia cordifolia* significantly lower serum levels of accumulated waste products BUN and creatinine is attributed to the enhanced GFR[20].

Regulate Oxalate Metabolism:

Hyperoxaluria is a most significant risk factor in the pathogenesis of renal stone. It has been reported that oxalate play an important role in stone formation and has about 15-fold greater effect than urinary calcium. Increased oxalate concentration is responsible for precipitation and deposition of CaOx crystals. Aqueous extract of *Tribulus terrestris* interfere with the metabolism of oxalate in male rats fed sodium glycolate.

Glycolate feeding results in hyperoxaluria as well as increased activities of oxalate synthesizing enzymes of the liver i.e., glycolate oxidase (GAO), glycolate dehydrogenase (GAD) and lactate dehydrogenase (LDH) and decreased kidney LDH activity. *T. terrestris* administration to sodium glycolate fed rats produced a significant decrease in urinary oxalate excretion, and a significant increase in urinary glyoxylate excretion, as compared to sodium glycolate fed animals and similar results were observed for *Aerva lanata*[21].

Antioxidant Activity (Free- Radical Scavengers/ Membrane Stabilization):

Renal cellular exposure to oxalate (Ox) and/or CaOx crystals leads to the production of Reactive Oxygen Species (ROS), development of oxidative stress followed by injury and inflammation. Renal injury and inflammation appear to play a significant role in stone formation. An overproduction of ROS and a reduction in cellular antioxidant capacities, due to down-regulated expression of the antioxidant enzymes (superoxide dismutase, catalase, glutathione peroxidase, and glucose-6

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phosphate dehydrogenase) as well as radical scavengers (vitamin E, ascorbic acid, reduced glutathione) leads to the development of Oxidative Stress (OS) [22].

Oxidative stress followed by renal cell injury and inflammation due to lipid peroxidation. Loss of membrane integrity subsequently facilitates the retention of calcium oxalate crystals and growth of stones in renal tubules. Recent studies have provided evidence that CaOx kidney stone patients malondialdehyde (MDA) in their urine, indicating ROS in kidneys of CaOx stone patients. Urinary excretion of these MDA is considered as a marker of renal epithelial cell injury. Recent studies evidenced that treatment with anti-oxidants and free radical scavengers reduced CaOx crystal induced renal injuries[23].

Herbal medicine or plants are rich source of natural antioxidants, can be used in treatment of hyperoxaluria induced oxidative stress and urolithiasis. Protective effect of *Paronychia argentea, B. ligulata* and *Trachyspermum ammi* in hyperoxaluric oxidative stress and CaOx crystal deposition is due to their potential antioxidant activity. *Quercus salieina, Achyranthus Aspera, Amni visnaga* and *Mimusops elengi* showed reduction in oxalate-induced renaltubular epithelial cell injury in cell culture due to their antioxidant activity[24] [25] [26]

Inhibition of ACE/Phospholipase A2:

ROS are produced from many sources and involve a variety of signalling pathways. Animal model studies have provided evidence for the hyperoxaluria-induced activation of the Renin-Angiotensin System (RAS); a major player in renal disease progression. RAS activate the NADPH oxidase in renal cells which is responsible for ROS production. Reduction of angiotensin II production by inhibiting ACE or blocking angiotensin receptors has been shown to significantly reduce renal CaOx crystal deposition as well as the development of interstitial inflammation. The ROS culminate phospholipase A2 activation through transcription factor NF--KB (nuclear factor NF-KB) as NF-KB can be activated by the stress of oxidants [27]and oxalate exposure also promotes rapid degradation of IxBa (an endogenous inhibitor of the NF-KB). The inhibition of the lipid peroxidation (decrease MDA level) after post treatment of plant extract can be attributed to decreased production of ROS due to inhibition of ACE or indirect inhibition of phospholipase A2 through inactivation of NF--KB. Many antioxidant constituents of plants like flavonoids reported to inhibitory activity on NF-KB gene expression. Some plants with antiurolithiatic property also reported to have ACE inhibition activity[28].

Antimicrobial Property:

Another antilithogenic effect of some herbal remedies is due to antimicrobial properties. It must be emphasized that a deficit in the crystallization inhibitory effect of urine and the presence of promoters are considered the most important risk factors in the process of urinary stone disease. When these conditions favour stone formation, the anti-adherent layer of GAGS acts as a protective barrier against urinary stone disease. If this layer is damaged, as a consequence of bacterial attack, a stone nucleus might develop, leading to a full stone in the urinary tract. At this point, some extracts that show antimicrobial properties can be considered antilithogenic by protecting the anti-adherent glycosaminoglycan layer covering the epithelium of the collecting system[29].

Renal stones often accompanied by infection (DTI's). Renal stones also contain matrix, a non-crystalline material. Then matrix content of a stone may be between 10 and 65% by weight and tends to be higher when there is an associated urinary tract infection. It has been suggested that alteration in the secretion of renal enzymes (decreased urokinase and increased sialidase) may increase matrix formation. Certain bacteria such as *Proteus mirabilis* and *Escherichia cob:,* alter urokinase/sialidase activity leading to matrix formation, in turn causing increased crystal adherence to the renal epithelium. Cystone also found to be effective in urinary tract infection and infective stones along with urolithiasis[30].

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Analgesic and Anti-Inflammatory Activity:

A patient with renal or ureteric colic from an obstructing stone typically presents with sudden onset of acute pain, often at night when the urine is maximally concentrated. Renal colic may be sudden or gradual in onset. The pain typically rises to a crescendo, causing the patient to writhe around and be unable to find a comfortable position[31]. In a clinical study, patients treated with Cystone reported a significant symptomatic relief from abdominal pain and dysuria. There was a significant reduction in the mean number of pain episodes from baseline to the end of the therapy[32] [33].

Some plants and plant products with Antiurolithiatic Activity:

- The effect of *C. nurvala* bark decoction on calcium oxalate urolithiasis induced by 3% glycolic acid has been studied in rats. The decoction showed significant activity in preventing the deposition of calcium and oxalate in the kidney by inhibiting the activity of the Liver enzyme glycolic acid oxidase. Treatment with *C. nurvala* bark decoction was reported to lower the levels of intestinal NaZ, KZ-ATPases[34].
- Investigations on the effect of *Ammi visnaga* seeds on kidney stones revealed that the antilithiatic effect is mainly because of highly potent diuretic activity and amelioration of uraemia and hyperbilirubinemia by seeds of *Ammi visnaga*[35]
- *Phyllanthus niruri* has an inhibitory effect on crystal growth, in a rat model of urolithiasis induced by introduction of calcium oxalate seed in bladder of rats. The effect may be due to higher Levels of glycosoamino glycans incorpated into calculi[36]. *In vitro* studies in which calcium oxalate precipitation was induced by addition of 0.1 M sodium oxalate to unfiltered urine samples from Wistar rats and normal humans in absence and presence of *P. niruri* extract (0.25 mg/ml), suggested that extract may interfere with early stages of stone formation[37].
- Fourteen patients with renal calculi and 16 patients with ureteric calculi have been treated with the herbomineral combination containing *Bergenia ligulata* and *Tribulus terrestris*. 28.57% of patients with renal calculi and 75% patients with ureteric calculi passed their calculi completely and in other patients there was a marked or partial expulsion of calculi along with changes in the shapes and sizes of calculi[38]
- The effect of ingestion of 3 and 10 g of tamarind pulp (*Tamarindus indicus*) was studied in normal subjects and in stone formers. Tamarind intake at the dose of 10 g showed significant beneficial effect in inhibiting spontaneous crystallization in both normal subjects and in stone formers[39]
- *Costus spiralis* is extensively used in Brazilian folk medicine for expelling urinary stones. Aqueous extract of *C. spiralis* when used at a dose of 0.25 and 0.5 g/kg / day for 4 weeks significantly reduced the growth of calcium oxalate calculi in the urinary bladder of rats[40]
- Antiurolithiatic activity of two compounds viz., 7-hydroxy2L, 4', 5L-trimethoxyisofLavone and 7-hydroxy-4L-methoxy isoflavone isolated from the heart wood of *Eysenhardtia polystachya* was studied in rats by observing calculus formation experimentally induced by zinc discs. A significant decrease in urinary stone size was observed in animals treated with these compounds[41]
- Experimental studies carried out on *Crataeva nurvala*, *Tribulus terrestris* and *Dolichos biflorus* showed them to be effective in preventing the deposition of stone material on glass beads in the urinary bladder of rats[42].All the three plants were shown to dissolve phosphate type of calculi in an in vitro model, where as oxalate, uric acid and cystine stones were not dissolved by *C. nurvala* and *D. biflorus* extracts. T. terrestris dissolved uric acid and cystine stones to some extent. Clinical studies carried out on *C. nurvala* showed that it changes the urinary chemistry of patients and thus it reduces the Lithogenic potential[43]

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- The aqueous extract of *Melia azedarach* Linn. was studied against ethylene glycol induced nephrolithiasis in male albino wistar rats. The aqueous extract of *M. azedarach* reduced urinary calcium, oxalate, phosphate and elevated urinary magnesium levels and urine volume[44]
- The seeds of *Dolichos biflorus* and rhizomes of *Bergenia ligulata* were tested for their in vitro antilithiatic and anticalcification activity by the homogenous precipitation method. The extracts were compared with an aqueous extract of cystone (a marketed preparation) for their activities. Also a combination of the extracts of the two plants was tested. Extracts of *Dolichus biflorus* showed activity almost equivalent to cystone while *Bergenia ligulata* showed less activity and the combination was not as active as the individual extracts[45]
- Phycocyanin a known antioxidant is reported to have potential antiurolithiatic activity as it reduces oxalate levels in kidney tissue significantly[46]
- The aqueous extract of Raphanus sativus showed antilithiatic activity on implants of calcium oxalate crystals or zinc discs in the urinary bladder of rats. The effect however is unrelated to increased diuresis or to a change of the muscarinic receptor affinity of the bladder smooth musculature to cholinergic ligands[47]
- The efficacy of the two Siddha drugs, *Aerva lanata* and *Vediuppu chunam* as antilithic agents were studied in rats using 0.75% ethylene glycol in drinking water as a urolithic rat model[48]
- The ethanolic extract of *Asparagus racemosus* Wild. had an inhibitory potential on lithiasis induced by oral administration of 0.75% ethylene glycolated water to adult male Albino Wistar rats for 28 days. The ethanolic extract, significantly reduced the elevated level of calculogenic ions in urine and it elevated the urinary concentration of magnesium, which is considered as one of the inhibitors of crystallization[49]
- The fresh juice of Leaves of *Plectranthus amboinicus* Lour. has effect against renal calculi particularly of calcium oxalate origin induced by administration of 1% ethylene glycolated water[50]
- The aqueous and alcoholic extracts of the root wood of *Moringa oleifera* Lam. significantly reduced the elevated urinary oxalate, showing a regulatory action on endogenous oxalate synthesis in hyperoxaluria induced with ethylene glycol.[51]

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