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PHCOG REV. : Short Review
Herbal Drugs in Urolithiasis - A Review

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ABSTRACT

The recent resurgence of plant remedies results from several factors like effectiveness of plant medicines and lesser side effects compared to modern medicines. In the present scenario, the need for basic scientific investigations on medicinal plants used in the indigenous systems becomes imminent. This is evident by the increase in number of reports by various investigators supporting the claims of medicinal plants and a dramatic increase in the share of plant products in pharmaceutical market. The present review aims to give data highlighting the present trends in research of medicinal plants accredited with antiurolithiatic activity. This may help investigators to identify and develop appropriate lead compounds or plant products beneficial in the management of urolithiasis.

KEYWORDS: Urolithiasis, renal calculi, calcium oxalate stones, magnesium ammonium phosphate stones, herbal drugs.

INTRODUCTION

Stone formation in the kidney is one of the oldest and most wide spread diseases known to man. Urinary calculi have been found in the tombs of Egyptian mummies dating back to 4000 BC (1) and in the graves of North American Indians from 1500-1000 BC (2). Reference to stone formation is made in the early Sanskrit documents in India between 3000 and 2000 BC (3).

Calcium-containing stones, especially calcium oxalate monohydrate (*Whewellite*), calcium oxalate dihydrate (*Weddellite*) and basic calcium phosphate (*Apatite*) are the most commonly occurring ones to an extent of 75-90% followed by magnesium ammonium phosphate (*Struvite*) to an extent of 10-15%, uric acid 3-10% and cystine 0.5-1% (4-6). In most of the cases the commonly occurring stones are calcium oxalate or magnesium ammonium phosphate type.

Many remedies have been employed during the ages to treat urinary stones. In the traditional systems of medicine, most of the remedies were taken from 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. The recent treatment procedures like surgical removal, percutaneous techniques and extracorporeal shock wave lithotripsy (ESWL) are prohibitively costly for the common man and with these procedures recurrence is quite common and the patient has to be subjected to careful follow up for a number of years. Pharmacotherapy can reduce the recurrence rate. The use of plant products with claimed uses in the traditional systems of medicine assumes importance.

An excellent account of the 'Pashanabheda' group of plants, claimed to be useful in the treatment of urinary stones is given by Narayana Swami and Ali (7), Bahl and Seshadri (8) and Mukerjee et al (9). In India, in the Ayurvedic system of medicine, Pashanabheda is the Sanskrit term used for a group of plants with diuretic and antiurolithiatic activities (Pashana=stone; Bheda=break). These reviews mainly discussed various plants accredited with diuretic and antiurolithiatic activities and their botanical identification. There is paucity of reviews on the pharmacological and clinical studies carried out on these plants with antiurolithiatic activity. Hence, in the present review an attempt has been made to enumerate the studies carried out on these plants. This could serve as a source of information on the present trends in research on plants accredited with antiurolithiatic activity.

Plants and plant products with antiurolithiatic activity

The marketed composite herbal formulations, Cystone (Himalaya Drug Company, India), Calcuri (Charak Pharmaceuticals, Bombay, India) and Chandraprabha bati (Baidyanath, India) 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 (10).

The alcoholic extract of *Bergenia ligulata* was found to be useful as curative in dissolving the calculi developed by foreign body insertion method using zinc discs in the bladder of albino rats against phosphate type of urolithiasis (11).

The Varuna bark - *Crataeva nurvala* has been extensively studied by a number of investigators in India. The Pharmacology division of Central Drug Research Institute, Lucknow, India has carried out detailed pharmacological and chemical studies on this plant. Studies have shown that ethanolic extract has a dose related antiurolithiatic activity in

albino rats induced by foreign body insertion method using glass beads (12). Lupeol, a triterpene compound has been isolated from C. *nurvala* and was shown to have dose related prophylactic and curative activities in albino rats when studied by foreign body insertion method using glass beads (13). Lupeol also showed a significant dose related antioxaluric and anticalciuric effects in rats against hydroxyproline-induced hyperoxaluria (14, 15). A number of lupeol derivatives have been synthesized and studied in rats for their antioxaluric and anticalciuric effects against hyperoxaluria (16). Some of these derivatives exhibited better antioxaluric and anticalciuric activity when compared to the parent compound lupeol.

The effect of C. *nurvala* bark decoction on calcium oxalate urolithiasis induced by 3% glycolic acid has been studied in rats (17). 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 Na^+, K^+-ATPases (18). C. *nurvala* was reported to be effective in the prophylaxis of oxalate urolithiasis induced by simultaneous administration of sodium oxalate and methionine in guinea pigs (19).

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 (20).

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 (21).

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 (22).

Antiurolithiatic activitiy of two compounds viz., 7-hydroxy-2',4',5'-trimethoxyisoflavone and 7-hydroxy-4'-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 (23).

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 (24). 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 (25).

The fresh juice of *Coleus aromaticus* was found to reduce the deposition of calcium and oxalate in the kidney of experimental rats (26). Certain enzyme systems implicated in the process of calcification like ATPases and phosphohydrolases were affected by the juice proving its regulatory influence on calcium oxalate stone formation.

Studies on various fractions of *Tribulus terrestris* have indicated that the aqueous methanolic fraction is more effective against experimentally induced urolithiasis by foreign body insertion method using glass beads in albino rats (27). Investigation of the effect of aqueous extract of *Tribulus terrestris* on the oxalate metabolism in male rats fed with sodium glycolate, revealed a decrease in urinary oxalate excretion and a significant increase in urinary glyoxylate excretion and also a decrease in liver GAO and GAD activities (28).

Studies on the stem juice of *Musa paradisiaca* were found to be effective in dissolving the phosphate type of stones in albino rats induced by foreign body insertion method using zinc discs (29). In another experimental study stem juice of *Musa* significantly reduced the incidence of oxalate urolithiasis by lowering the activity of the enzyme glycolic acid oxidase (30). The stem juice of *Musa* reduced urinary oxalate, glycolic acid, glyoxylic acid and phosphorus excretion in hyperoxaluric rats (31).

Grases and co-workers of Division of Urochemistry, Department of Chemistry, University of Balaeric Islands, Spain have studied the antiurolithiatic activity of *Zea mays, Rosa canina, Herniaria hirsuta* and *Agropyron repens* in rats. The antiurolithiatic activity of Z. *mays* has been assigned to its diuretic activity (32). *R. canina* was found to have significant activity on calcium oxalate urolithiasis as it decreased calciuria and increased citraturia (33). The antiurolithiatic activity of *H. hirsuta* has been assigned to increase in citraturia (34), where as *A. ripens* did not show any positive effects on the risk factors of urolithiasis (34). The effect of *H. hirsuta* on the adhesion of calcium oxalate monohydrate crystals to renal cells was studied which indicated that *H. hirsuta* altered crystal adhesion only under conditions of increased fluidity (35).

Ahsan and coworkers have investigated the antiurolithiatic activity of some Saudi Arabian folklore plants viz., *Petroselinum sativum, Tachyspermum ammi, Alpinia galanga, Ammi majus* and *Trigonella foenum-graceum* against calcium oxalate urolithiasis induced by 3% glycolic acid. *P. sativum* and *T. foenum-graceum* were found to reduce calcium oxalate urolithiasis, *T. ammi* and *A. galanga* were found to be less effective, where as the seeds of A. *majus* did not show any activity (36, 37).

Studies carried out on the roots of *Rubia tinctorum,* was found to be effective against stones of oxalate, phosphate, calcium carbonate and uric acid. This activity was attributed to the presence of hydroxy anthraquinones and their derivatives (38). *R. tinctorum* was shown to expel the stones by stimulating the smooth muscles of the urinary bladder.

Studies were carried out on several Indian medicinal plants in our laboratory at Manipal and Tirupati. The plants studied were *Aerva lanata, Ammannia baccifera, Asteracantha longifolia, Homonia riparia, Imperata cylindrica, Mimosa pudica* and *Rotula aquatica*. The studies were carried out in male albino rats. Foreign body insertion method using zinc discs was employed for inducing magnesium ammonium phosphate type of stones and 3% glycolic acid along with normal rat feed was fed for inducing calcium oxalate urolithiasis. Some of these plants showed promising results against magnesium ammonium phosphate and/ or calcium oxalate type of stones. The plants that showed promising antiurolithiatic activity are discussed below.

Ethanolic extract of *Ammania baccifera* was found to be effective as prophylactic and curative against phosphate type of stones (39). Ethanolic extract of roots of *Homonia riparia* has effective prophylactic and curative activity against calcium oxalate and struvite stones (40). Ethyl acetate extract of *Rotula aquatica* showed significant antilithic activity against *struvite* stones and calcium oxalate stones (41).

The studies on *A. lanata* employing zinc discs implants in urinary bladder of rats and also administration of 1% ethylene glycol orally for four weeks did not effect the formation or dissolution of phosphate type of stones. This study showed that calcium oxalate stones might not be formed on zinc discs/ foreign body when the urine pH is alkaline (42). In other similar studies using combination of zinc disc and ethylene glycol (1%) for four weeks *Mimosa pudica* Linn. was not effective in either preventing stone deposition or dissolving preformed stones (43). There was no significant influence of electrolytes or metabolic products on the uroliths.

Christina and coworkers has extensively studied modulatory effect of roots of *Cyclea peltata* Lam. on stone formation and antilithic effect of decoction of *Rotula aquatica* (44). *C.peltata* root powder decreased urinary oxalate, calcium, serum potassium likewise increased serum magnesium levels (45).

Cranberry juice has antilithogenic properties as its ingestion significantly and uniquely altered urinary risk factors causing decreased excretion of oxalate and phosphate while increase in citrate excretion was noted (46).

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* (47).

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 glycosoaminoglycans incorpated into calculi (48). *In vitro* studies in which calcium oxalate precipitation was induced by addition of 0.1M 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 (49).

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 (50).

Phycocyanin a known antioxidant is reported to have potential antiurolithiatic activity as it reduces oxalate levels in kidney tissue significantly (51).

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 (52).

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 (53).

The ethanolic extract of *Asparagus racemosus* Willd. 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 (54).

The fresh juice of leaves of *Plectranthus amboinicus Lour*. has effect against renal calculi particulary of calcium oxalate origin induced by administration of 1% ethylene glycolated water (55).

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 (56).

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 (57).

CONCLUSION

The vast Ayurvedic literature claims a number of plants to be useful in urinary stones; still many plants need to be exploited for their pharmacological actions. Inspite of intensive research to establish the mechanisms of stone formation, dietary management, evaluation of medicinal plants and other agents in the treatment of urinary stones, still to date there is no standard drug available. The main drawbacks in the development of a standard drug may be the multicausal nature of urolithiasis, different biochemical disorders that leads to urolithiasis and different chemical varieties of renal stones.

As the present review illustrates, a number of medicinal plants are evaluated mainly against calcium oxalate and

magnesium ammonium phosphate types of kidney stones, employing various experimental models of urolithiasis. Most of these studies were preliminary, carried out in animals and are not sufficient for the development of a pharmaceutical product. Still, intensive preclinical and clinical studies are required to evaluate the efficacy and toxicity of these plant products. Further, chemical studies of the plants are needed to isolate the active principles and investigate them in order to identify a promising lead compound.

Currently, in the management of urinary stones surgical procedures and extra corporeal shock wave lithotripsy are commonly employed. The major drawback of these procedures is recurrence of stones. The plant products and derivatives of their lead compounds as such may not replace these procedures but may surely help in decreasing the recurrence rate of renal calculi.

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