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Establishing the Principle of Herbal Therapy for Antiurolithiatic Activity: A Review

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ABSTRACT

A wide range of plants and plant-derived products are used in folk medicine for the treatment of urolithiasis as a prophylactic agent or as curative agent. Most of them found to be effective, but still the complete mechanism of action of these herbal drugs remains to be unclear. In present review we are discussing the various mechanism of action through which phytotherapeutic agents exert their antiurolithiatic effect. Unlike allopathic medicines which targets only one aspect of urolithiatic pathophysiology, most of plant based therapy have been shown to be effective at different stages of stone pathophysiology. Currently known herbal drugs exert their antilithogenic properties by altering the ionic composition of urine viz.; decreasing the calcium and oxalate ion concentration or increasing magnesium and citrate excretion. Most of these remedies also express diuretic activity or lithotriptic activity. Some of the herbal drugs reported to disaggregate of mucoproteins, which are actually binds the crystal to the renal cells. Some medicinal plants contain chemical compounds like Glycosaminoglycans (GAGs) which themselves possess an inhibitory effect in the crystallization of calcium oxalate. Antioxidant constituents of the plants also help in ameliorating the crystal/oxalate induced renal cell injury. Thus, antiurolithiatic activity of plants or herbal formulation may be due to synergism of their diuretic activity, crystallization inhibition along with antioxidant activity.

Key words: Renal stone, phytotherapy, urolithiasis, traditional medicine

INTRODUCTION

Urolithiasis is a recurrent renal disease affects 4-8% in UK, 15% in US, 20% in Gulf countries and 11% population in India. Stone formation tends to recur at very high rate; without preventative measures after a first stone. After 3 years this is about 40%, by 10 years up to 75% and by 25 years virtually every patient has formed at least one more stone (Leye *et al.*, 2007). There are several types, most commonly consisting of calcium phosphates and calcium oxalates; others are composed of magnesium ammonium phosphate (struvite), uric acid or cystine (Sellaturay and Fry, 2008). Epidemiological data suggests that 60-80% of stone is composed mainly of calcium oxalate (CaOx). Stones formation occurs when urinary concentrations of stone forming salts, exceed the limit of metastability for that salt in solution. This most often reflects excessive excretion of one or more stone constituents, deficient inhibitory activity in urine, or simply a low urine volume resulting in excessively concentrated urine (Steven, 2003).

The pathogenesis of calcium oxalate stone formation is a multi-step process, which includes-nucleation, crystal growth, crystal aggregation and crystal retention (Pareta *et al.*, 2011). Various substances in the body have an effect on one or more of the above stone forming processes, thereby influencing a person's ability to promote or prevent stone formation. Promoters of stone formation facilitate stone formation whilst inhibitors prevent it. Low urine volume, low urine pH, calcium, sodium, oxalate, and urate are known to promote stone formation (Basavaraj *et al.*, 2007).

Various therapies including thiazide diuretics and alkali-citrate are being used in attempt to prevent recurrence of hypercalciuria and hyperoxaluria-induced calculi but scientific evidence for their efficacy is less convincing (Bashir and Gilani, 2008). Endoscopic stone removal and Extracorporeal Shock Wave Lithotripsy (ESWL) have revolutionized the treatment of urolithiasis but do not prevent the likelihood of new stone formation. These recent treatment procedures for renal stone 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 (Prasad *et al.*, 2007). Even improved and high cost treatment of ESWL in therapeutic doses may cause acute renal injury, decrease in renal function, and an increase in stone recurrence. In addition, persistent residual stone fragments and possibility of infection after ESWL represent a serious problem in the treatment of stones (Begun *et al.*, 1991).

Urolithiasis is still a mysterious disease even after extensive research in Urology. Sophisticated instruments, investigations etc., have failed to trace out the exact cause and mechanism of urolithiasis. But, few researches conducted in recent times revealed various factors, which are responsible in manifesting this condition. The treatment for this condition in modern medicine is not only expensive but also not easily affordable to the needy poor. Actually, there are no satisfactory drugs in modern medicine, which can dissolve the stone and the physicians remains to be depend on alternative systems of medicine for better relief (Galib *et al.*, 2006).

Herbal medicines are efficacious and have lesser side effects compared to modern medicines and also reduce the recurrence rate of renal stone (Prasad *et al.*, 2007). Although the complete mechanism of action of these remedies are lacking but, plant based phytotherapeutic agents represent the majority used in medicine for urolithiasis. Unlike allopathic medicines which targets only one aspect of urolithiatic pathophysiology, most of plant based therapy have been shown to be effective at different stages of stone pathophysiology. Currently known extracts exert their antilithogenic properties by altering the ionic composition of urine eg., decreasing the calcium ion concentration or increasing magnesium and citrate excretion. These remedies can also express diuretic activity or lithotriptic activity. Drugs with multiple mechanisms of protective action may be one way forward in minimizing tissue injury in human disease (Barry, 1991). Herbal medicines have several phytoconstituent and exert their beneficial effects urolithiasis by multiple mechanisms like:

- Helps in spontaneous passage of calculi by increasing urine volume, pH and anti-calcifying activity (Diuretic activity)
- Balance the Inhibitor and promoter of the crystallization in urine and affects the crystal nucleation, aggregation and growth (Crystallization inhibition activity)
- Relieves the binding mucin of calculi (lithotriptic activity)
- Improved 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)

The above mentioned mechanism schematically represented in Fig. 1 and described briefly here along with plants or phytotherapeutic agent exert their mechanism in particular way (Table 1).

DIURETIC AND LITHOTRIPTIC ACTIVITY

In herbal treatment of kidney stones, antilithics are used to “dissolve” the stones or aid their passing to guard against further retention. Diuretic action is also needed to increase the amount of fluid going through the kidneys and flush out the deposits (Gohel and Wong, 2006). Lithotriptic means breaking and disintegrating or dissolution of the preformed stones. Some of the herbal drugs reported to disaggregate of mucoproteins, which are actually binds the crystal to the renal cells. Stones occur when urinary chemistry results in increase concentrations of stone salts (oxalate, Calcium, Phosphates) that leads to super-saturation (SS) and exceeds the limit of metastability for that salt in solution (Steven, 2003). Increase urine volume decreases the saturation of the salts and prevents the precipitation of the crystal at physiological pH. All herbal medicine used for the treatment of the urolithiasis also has diuretic action and some known to alkalize the urine. In-vivo studies shown that *Amni visnaga*, *Zea mays*, *Raphanus sativus* and *Vediuppu chunnam* exert their antiurolithiatic effect mainly through diuresis (Table 1). (Khan *et al.*, 2001; Grases *et al.*, 1993; Vargas *et al.*, 1999; Selvam *et al.*, 2001).

CRYSTALLIZATION INHIBITION

Inhibitors are defined as molecules that increase the SS required to initiate nucleation, decrease crystal growth rate and aggregation, and inhibit secondary nucleation. In contrast promoters reduce the formation product of the supersaturated solution. Some of the common promoters are oxalate, calcium, cystine, uric acid and inhibitors are citrate and magnesium (Mazumdar *et al.*, 2009). An imbalance between urinary-promoting and inhibiting factors has been suggested as more important in urinary stone formation than a disturbance of any single substance. Various physiological inhibitors of urolithiasis found in urine including inorganic (e.g., magnesium) and organic (e.g., Citrate, Urinary prothrombin fragment, GAGs and other macromolecule) substances are known to inhibit stone formation. Organic inhibitory compounds adsorb to the surface of the crystal, thereby inhibiting crystal nucleation, growth and aggregation (Basavaraj *et al.*, 2007). Interference with crystal growth and aggregation therefore seems a possible therapeutic strategy for the prevention of recurrent stone disease. The medicinal plants contain chemical compounds like Glycosaminoglycans (GAGs) which themselves possess an inhibitor effect in the crystallization of calcium oxalate. Macromolecule of higher molecular weight of plant extract excerpts their action similar to natural urinary inhibitors and inhibits crystal nucleation, growth and aggregation (Atmani *et al.*, 2003). Grapefruit and Lemon juice (Trinchieri *et al.*, 2002; Seltzer *et al.*, 1996) reported to increases urinary citrate excretion thus

Table 1: Various phytotherapeutic agents used for the treatment of urolithiasis and their probable mechanism of action

Phytotherapeutic agent	Type of study	Probable mechanism of action	References
<i>Herniaria hirsuta</i>	<i>In vitro</i> , cell culture, <i>in vivo</i>	Eliminate preexisting kidney stones, decrease crystal size and increase COD, Diuretic	Atmani and Khan, (2000); Atmani <i>et al.</i> (2003); Atmani <i>et al.</i> (2004);
<i>Amni visnaga</i>	<i>In vivo</i> animals, cell culture	Potent diuretic, khellin and visnagin prevent renal epithelial cell damage caused by oxalate and COM	Khan <i>et al.</i> (2001); Vanachayangkul <i>et al.</i> (2010)
<i>Tribulus terrestris</i>	<i>In vitro</i> , cell culture, <i>in vivo</i> animals	Crystal (COM) growth inhibition, prevent renal epithelial cell damage, decrease oxalate excretion by affecting oxalate metabolism	Joshi <i>et al.</i> (2005); Aggarwal <i>et al.</i> (2010b); Sangeeta <i>et al.</i> (1994)
<i>Bergenia ligulata</i>	<i>In vitro</i> , <i>in-vivo</i> animals	Crystal (COM) growth inhibition, decreases calcium phosphate nucleation, CaOx crystal lyzation inhibition, diuretic, hypermagneseuric and antioxidant effects	Garimella <i>et al.</i> (2001); Joshi <i>et al.</i> (2005); Bashir and Gilani. (2008)
<i>Dolichos biflorus</i>	<i>In vitro</i>	Decrease crystal preception	Garimella <i>et al.</i> (2001)
<i>Aerva lanata</i>	<i>In vivo</i> animals	Decreases urinary calcium, oxalate, uric acid and phosphorus excretion, diuretic, roxalate metabolism by reducing level of oxalate synthesizing enzyme.	Selvam <i>et al.</i> (2001); Soundararajan <i>et al.</i> (2006)
<i>Vediuppu chunnam</i> (Polyherbal formulation)	<i>In vivo</i> animals	Diuretic, decreases urinary calcium, oxalate, uric acid and phosphorus excretion	Selvam <i>et al.</i> (2001)
<i>Raphanus sativus</i>	<i>In vivo</i> animals	Diuretic	Vargas <i>et al.</i> (1999)
<i>Moringa oliefera</i>	<i>In vivo</i> animals	Diuretic, decrease urinary oxalate, Improved renal function, dissolve preformed stones and prevent new stone formation	Karadi <i>et al.</i> (2006)
<i>Costus spiralis</i>	Animals <i>in vivo</i>	Decreases stone size with unknown Mechanism unrelated to diuretic action	Viel <i>et al.</i> (1999)
<i>Achyranthus Aspera</i>	<i>In vitro</i> , cell culture, Animals <i>in vivo</i>	Inhibit crystal nucleation and growth, prevent renal epithelial cell damage, diuretic, reduced urinary excretion of calcium and oxalate	Aggarwal <i>et al.</i> (2010b)
<i>Quercus salicina</i>	Cell culture	Reduction in oxalate-induced renal epithelial cell injury	Moriyama <i>et al.</i> (2007)
<i>Phyllanthus niruri</i>	<i>In vitro</i> , <i>in vivo</i> animals	Inhibit crystal aggregation and growth, interfered crystal morphology, probably by modifying the crystal-crystal and/or crystal-matrix interactions. Antispasmodic and relaxant	Barros <i>et al.</i> (2003), (2006); Melo <i>et al.</i> (1992); Paulino <i>et al.</i> (1996)
<i>Cranberry juice</i>	Humans <i>in vivo</i>	Increases urinary citrate excretion, decreases urinary oxalate and calcium excretion	McHarg <i>et al.</i> (2003)
<i>Cynodon dactylon</i>	<i>In vivo</i> animals	Decrease crystal size and increase COD as compare to COM	Atmani <i>et al.</i> (2009)
<i>Grapefruit juice</i>	Humans <i>in vivo</i>	Increases urinary citrate excretion	Trinchieri <i>et al.</i> (2002)
<i>Paronychia argentea</i>	<i>In vivo</i> animals	Lowering of urinary concentrations of stone forming constituents, antioxidant activity	Bouanani <i>et al.</i> (2010)
<i>Lemonade juice</i>	Humans <i>in vivo</i>	Increases urinary citrate excretion	Seltzer <i>et al.</i> (1996)
<i>Pyracantha crenulata</i>	<i>In vivo</i> animals	Increase diuresis and lowering of urinary concentrations of stone forming constituents.	Bahuguna <i>et al.</i> (2010)
<i>Trachyspermum ammi</i>	<i>In vivo</i> animals	Maintain renal functioning, reduce renal injury and decrease crystal excretion in urine and retention in renal tissues	Kaur <i>et al.</i> (2009)

Table 1: Continue

Phythereapeutic agent	Type of study	Probable mechanism of action	References
<i>Mimusops elengi</i>	<i>In vivo</i> animals	Lowers excretion of calcium and oxalate, diuretic, antioxidant effect prevent renal cell injury	Ashok <i>et al.</i> (2010)
<i>Cystone</i> (Polyherbal formulation)	<i>In vivo</i> animals, Humans <i>in vivo</i>	Crystallo-colloid balance, Antimicrobial, Antispasmodic	Mitra <i>et al.</i> (1998); Kumaran <i>et al.</i> (2007)
<i>Solidago virgaurea L.</i>	Animals <i>in vivo</i>	anti-inflammatory and antimicrobial	Melzig 2004.
<i>Rubia cordifolia</i>	Animals <i>in vivo</i>	antioxidant and decrease urinary concentration of stone-forming constituents	Divakar <i>et al.</i> (2010)
<i>Arctium lappa</i>	Animals <i>in vivo</i>	Prevents kidney epithelium microcalculous retention, antiseptic	Gurocak and Kupeli (2006); Grases and Costa-Bauza (1990)
<i>Boerhaavia diffusa</i>	Animals <i>in vivo</i>	Diuretic, lowers excretion of calcium and oxalate	Pareta <i>et al.</i> (2010)

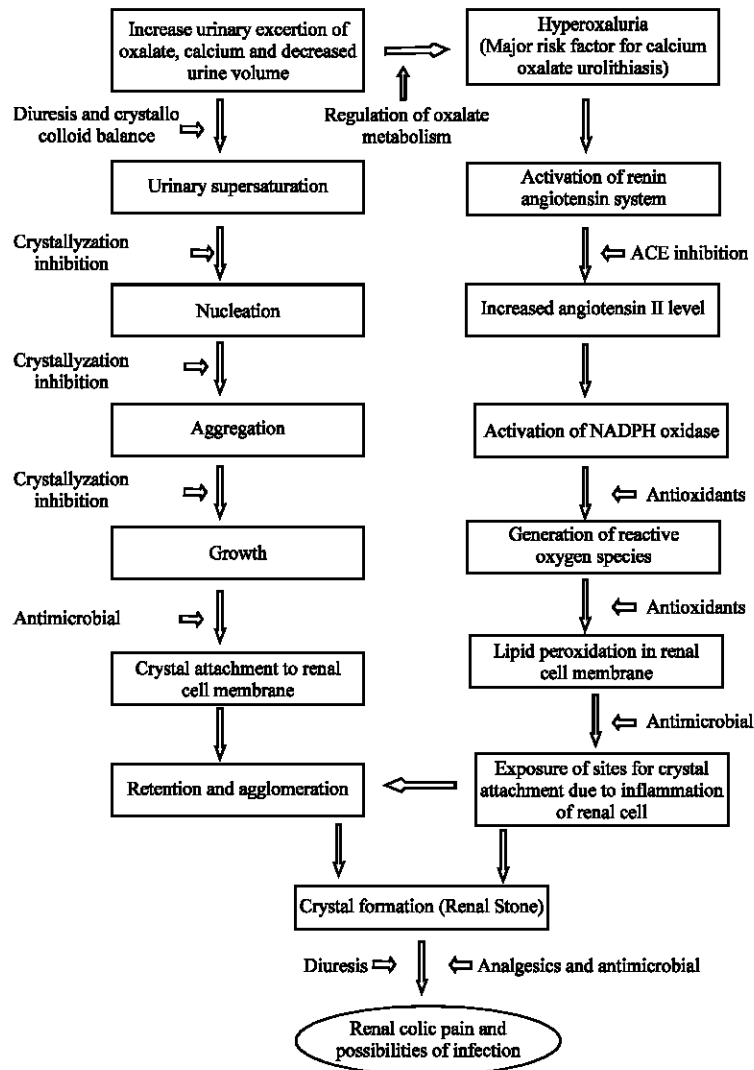


Fig. 1: Probable mechanism of action of Phytotherapeutic agents (most of plant based therapy shows their effectiveness at different stages of stone pathophysiology)

exerting their crystallization inhibition effect *in-vivo* as well as *in-vitro* probably through formation of calcium citrate which is more soluble than CaOx. *B. ligulata*, *A. indica* and *H. hirsuta* also exert their antilithogenic effect through crystal growth inhibition (Table 1) (Bashir and Gilani, 2008; Pareta *et al.*, 2011; Atmani and Khan, 2000).

REGULATES THE CRYSTALLOID COLLOID IMBALANCE AND IMPROVE RENAL FUNCTION

In urine there are a number of crystalloids 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. 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.

An increase in urinary phosphorus excretion was observed in ethylene glycol induced urolithic rats. Increased excretion of phosphorus has been reported in stone formers (Soundararajan *et al.*, 2006). 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 (Karadi *et al.*, 2006; Soundararajan *et al.*, 2006; Selvam *et al.*, 2001). Increased excretion of uric acid has been reported in stone formers and hyperoxaluric rats. Uric acid interferes with calcium oxalate solubility and it binds and reduces the inhibitory activity of GAGs (Selvam *et al.*, 2001). 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 (Selvam *et al.*, 2001; Soundararajan *et al.*, 2006). *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 (Table 1) (Divakar *et al.*, 2010; Soundararajan *et al.*, 2006; Karadi *et al.*, 2006; Mitra *et al.*, 1998).

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 (Ghodkar, 1994). Herbal therapy improves the renal function by increasing the excretion of urea and creatinine. Most of the phytotherapeutic agent exerts their antiurolithiatic effect through this mechanism (Fig. 1). *Moringa oleifera* and *Rubia cordifolia* significantly lower serum levels of accumulated waste products BUN and creatinine is attributed to the enhanced GFR (Table 1) (Karadi *et al.*, 2006; Divakar *et al.*, 2010).

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 (Karadi *et al.*, 2006; Soundararajan *et al.*, 2006). 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 resulted 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 (Sangeeta *et al.*, 1994) and similar results were observed for *Aerva lanata* (Soundararajan *et al.*, 2006).

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 phosphate dehydrogenase) as well as radical scavengers (vitamin E, ascorbic acid, reduced glutathione) leads to the development of Oxidative Stress (OS) (Khan, 2005; Rodrigo and Bosco, 2006). 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 (Selvam, 2002). Recent studies have provided evidence that CaOx kidney stone patients malondialdehyde (MDA) in their urine, indicating ROS in kidneys of CaOx stone patients (Huang *et al.*, 2003; Puntel *et al.*, 2007). 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. Pre-treatment with vitamin E along with mannitol abolished the deposition of CaOx crystals in the kidneys of rats injected with sodium oxalate (Thamilselvan and Selvam, 1997). Alanine-induced deposition of CaOx crystals in rat kidneys was blocked by dietary supplementation with vitamin E plus selenium (Kumar and Selvam, 2003). These antioxidant therapies restore the activity of antioxidant enzymes and free radical scavengers. Therefore, treatments with natural antioxidants and free radical scavengers, seems to possible therapeutic strategy for ameliorating hyperoxaluria induced oxidative stress and renal cell injury in urolithiasis. 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* (Bouanani *et al.*, 2010; Bashir and Gilani, 2009; Kaur *et al.*, 2009) in hyperoxaluric oxidative stress and CaOx crystal deposition is due to their potential antioxidant activity. *Quercus salicina*, *Achyranthus Aspera*, *Amni visnaga* and *Mimusops elengi* shown reduction in oxalate-induced renal tubular epithelial cell injury in cell culture due to their antioxidant activity (Table 1) (Moriyama *et al.*, 2007; Aggarwal *et al.*, 2010a; Vanachayangkul *et al.*, 2010; Ashok *et al.*, 2010).

INHIBITION OF ACE/ PHOSPHOLIPASE A₂

ROS are produced from many sources and involve a variety of signaling 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 (Khan, 2004; 2005).

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 (Toblli *et al.*, 2002). The ROS culminate phospholipase A₂ activation through transcription factor NF-κB (nuclear factor NF-κB) (Lappas *et al.*, 2004), as NF-κB can be activated by the stress of oxidants (Siebenlist *et al.*, 1994). And oxalate exposure also promotes rapid degradation of IκBα (an endogenous inhibitor of the NF-κB) (Joshi *et al.*, 2005). 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-κB. Many antioxidant constituents of plants like flavanoids reported to inhibitory activity on NF-κB gene expression. Some plants with antiurolithiatic property also reported to have ACE inhibition activity.

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.

Renal stones often accompanied by infection (UTI'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 coli*, alter urokinase/sialidase activity leading to matrix formation, in turn causing increased crystal adherence to the renal epithelium (Sellaturay and Fry, 2008). Cystone also found to be effective in urinary tract infection and infective stones along with urolithiasis (Table 1) (Kumaran *et al.*, 2007).

ANALGESIC AND ANTI-INFLAMMATORY ACTIVITY

A patient with renal or ureteric colic from an obstructing stone typically presents with sudden onset of acute loin 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 (Leye *et al.*, 2007). 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. Cystone exhibited a good spasmolytic activity on the smooth muscles of the rabbits and guinea pigs (Phukan *et al.*, 1977; Kumaran *et al.*, 2007). *Solidago virgaurea* and *Phyllanthus niruri* (Melzig, 2004) have their beneficial action in urolithiasis due to anti-inflammatory effect (Table 1).

CONCLUSION

An increasing interest and use of herbal or plant based medicine is apparent worldwide and especially in Western countries in recent years. These plant based therapy used as adjunct therapy particularly in urolithiasis as there are no satisfactory drugs in modern medicine which can dissolve the stone and the physicians remain to be depend on alternative systems of medicine for better relief. Currently known herbal drugs exert their antilithogenic effect by altering the ionic composition of urine, e.g., decreasing the calcium and oxalate ion concentration or increasing magnesium and citrate excretion. Most of these remedies also express diuretic activity or lithotriptic activity. Some of the herbal drugs reported to disaggregate of mucoproteins, which are actually binds the crystal to the renal cells. Some medicinal plants contain chemical compounds like GAGs which themselves possess an inhibitory effect in the crystallization of calcium oxalate. Antioxidant constituents of the plants also help in ameliorating the crystal/oxalate induced renal cell injury. Thus, antiurolithiatic activity of plants or herbal formulation may be due to synergism of their diuretic activity, crystallization inhibition along with antioxidant activity. Although these herbal medicine are popular in folk culture but rationale behind their efficacy and safety are not well established. Only a few studies have suggested some evidence for the efficacy of herbal medicines, however, most are not evidence-based. Some preclinical research has proved the efficacy of some of these herbs in urolithiasis. Precise understandings of the pathophysiology of disease and mechanism of action of these herbal medicines have great importance in development of effective and safe antiurolithiatic agent. In this respect the absence of this information provide a fruitful area for scientific research by willing investigators.

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