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Review Article
Urolithiasis: Critical Analysis of Mechanism of Renal Stone Formation and Use of Medicinal Plants as Antiurolithiatic Agents

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Abstract
Urolithiasis is one of the important constraints in livestock as well as human health globally since last decades. With its multi-factorial etiology, high rate of reoccurrence and treatment failure, urinary stone diseases provides a medico-vet challenge. In spite of substantial progress in the study of physiological manifestation of urolithiasis, its exact mechanism is still not clearly understood. The recent proposed mechanism of stone formation involves urinary supersaturation, crystal nucleation, precipitation, growth, aggregation of crystals and their retention in renal tubular epithelial cells. There is no satisfactory drug available for the treatment of urolithiasis, especially for the prevention of its recurrence. At present time conventional treatments including alkali therapy, thiazide diuretics and allopurinol are somewhat effective for various types of urolithiasis, but none of them are 100% effective. Medicinal plants have also been used as an alternative therapy for both prevention and treatment of kidney stone diseases since ancient Vedic era. Now-a-days various researchers also shifted towards medicinal plants for evaluating their antiurolithiatic efficacy but, most of the plants were yet to be scientifically validated. This review presents a comprehensive account of the mechanism of renal stone formation, role of inhibitors and promoters in calcium oxalate crystallisation as well as its risk factor analysis and use of medicinal plants as antiurolithiatic agent in animals.

Key words: Urolithiasis, medicinal plants, calcium oxalate, promoters, inhibitors, risk factors

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INTRODUCTION

Urolithiasis is one of the important constraints in livestock as well as human health globally since last decades, irrespective of geographical, racial and cultural boundaries (Aggarwal *et al*., 2013). It is also considered as the third most common problem of urinary tract (Bashir *et al*., 2010; Sayana *et al*., 2014). Urolithiais was coined from two Greek words "Ouron" means urine and "Lithos" means stone, hence literary means formation of stone anywhere in urinary tract. Urolithiais generally includes nephrolithiasis (Renal calculi or kidney stones), Ureterolithiasis (Ureter calculi) and cystolithiasis (Bladder calculi). Urinary stones are one of the major problems and an important cause of morbidity and end stage renal failure in India. Raising of animals in highly intensive system of farming, feeding high amount of concentrate diet for augmenting growth and production traits, increase the incidence of urolithiasis to many folds in farm animals now-a-days. With its multi-factorial etiology and high rate of reoccurrence urinary tract stone diseases need medico-vet challenges. There is thus an urgent need to prevent this disease before its occurrence.

In spite of substantial progress in the study of the biological and physical manifestation of urolithiasis, there is no satisfactory drug available for the treatment of urolithiasis, especially for the prevention of recurrence of the stones (Moe *et al*., 2011). At present time, conservative measures like increased fluid intake to ensure sufficient urinary dilution and conventional treatments including alkali therapy, thiazide diuretics and allopurinol are somewhat effective for various types of urolithiasis, but none of them are 100% effective (Sakhaee, 2009a). Medicinal plants also have been used as an alternative therapy for both prevention and treatment of kidney stone diseases since ancient Vedic era. Now-a-days various researchers also shifted towards medicinal plants for evaluating their antiurolithiatic efficacy (Dinesh *et al*., 2013). But, most of the plants used by ancient people were still not scientifically validated (Mikawlrawng and Kumar, 2014). The present review deals with the pathophysiology of urolithiasis with special reference to calcium oxalate stone as well its risk factor analysis and management in animals.

TYPES OF CRYSTALS

Urinary stones are polycrystalline aggregates consisting of varying amounts of crystal and organic matrix components. Stone matrix accounts for only 2-3% of the dry weight (Aggarwal *et al*., 2013) of urolith and consists of various macromolecules like proteins (64%), nonamino sugars (9.6%), hexosamine as glucosamine (5%), bound water (10%) and rest as bound ash (Boyce, 1968). Lipid has also been shown to be an important component of stone matrix (Khan *et al*., 1988). The type of minerals in uroliths can be readily identified by optical crystallography, infrared spectroscopy and/or x-ray diffraction. Oxalate, struvite, urate and cystine are the important crystals mostly present in livestock and companion animals (Houston and Moore, 2009; Bartges *et al*., 2004; Parrah *et al*., 2010).

Globally, calcium oxalate is considered as the main constituent in the renal calculi (Khan, 2014). Calcium containing stones, especially Calcium Oxalate Monohydrate (COM) also known as whewellite, Calcium Oxalate Dehydrate (COD) also known as weddellite, and basic calcium phosphate (apatite) are the most commonly occurring stones to an extent of 75-90% followed by magnesium ammonium phosphate (struvite) to an extant of 10-15%, uric acid 3-10% and cystine 0.5-1% in human being (Harsoliya *et al*., 2011). Silicate stones or drug induced stones are very rarely seen in human and can be a result of taking certain medications or herbal products and the subsequent build-up of chemicals from those products in the urine (Osborne *et al*., 2009).

PREDISPOSING FACTORS (RISK FACTORS)

Kidney stone formation or urolithiasis is a complex process that occurs due to imbalance between promoters and inhibitors in the kidneys or urinary tract (Aggarwal *et al*., 2013). Diet or feed, life style, soil, geographical region, pH of urine, etc., may be considered as important predisposing factors affecting stone formation (Radostits *et al*., 2010).

Urolithiasis in ruminant is considered primarily as a nutritional disease. The prevalence of urolithiasis in the USA is highest in calves, lambs and kids castrated at an early age and fed high grain diets with roughly 1:1 calcium: phosphorus ratio or a diet high in magnesium. Ruminants fed high grain diets with low calcium:phosphorus ratio is at increased risk of developing struvite uroliths, whereas ruminants grazing on silica-rich soil are predisposed to form silica uroliths (Radostits *et al*., 2010). Diets high in calcium may result in calcium carbonate uroliths, while plants such as halogeton or tops from the common sugar beet may be a factor in calcium oxalate formation. The mineral composition of water along with dietary mineral imbalances, probably contributes more to initiating urolith formation than the lack of water itself.

A definitive diagnosis of urolithiasis in a single animal suggests that all males in the population are at risk of the disease. The distal aspect of the sigmoid flexure of cattle and the sigmoid flexure and urethral process of sheep and goats

are the most common sites for uroliths to lodge (Tiruneh, 2000). Irritation at the site of lodging causes inflammation and swelling that contributes to urethral occlusion. Castration of young males also predisposes to urolith induced urethral obstruction by removing hormonal influences necessary for mature development of the penis and urethra.

MECHANISM OF CALCIUM OXALATE STONE FORMATION

In spite of substantial progress in the study of physiological manifestation of urolithiasis, its exact mechanism is still not clearly understood (Coe *et al*., 2010). The recent proposed mechanism of stone formation involves urinary supersaturation, crystal nucleation, precipitation, growth, aggregation of crystals and their retention in renal tubular epithelial cells, including the adhesion or endocytosis of crystals by the renal cells (Aggarwal *et al*., 2013; Khan *et al*., 2012a).

Urinary supersaturation: Urine is a highly saturated solution containing various crystalloids and colloids, but does not precipitate under normal condition due to presence of protective stone forming inhibitors. Supersaturation is considered as an important driving force for crystallization in urine (Pak *et al*., 2004). When a salt is added to a solvent it dissolves in the solvent until a particular concentration is reached, beyond which no further dissolution is possible. At this point, the solvent is said to be saturated with the salt. If more salt is added, it crystallizes in solution, provided the temperature and pH are unchanged (Carvalho and Nakagawa, 1999).

Formation of nidus (Crystal Nucleation): The initial step in the transformation from a liquid to a solid phase in a supersaturated solution is called nucleation. Nuclei form the first crystals that do not dissolve and have a characteristic lattice pattern. In urine, nuclei usually form on existing surfaces. Epithelial cells, urinary casts, RBCs and other crystals can act as nucleating centers in urine (Smith, 1990). Once a nucleus is created and principally if it is anchored, crystallization can occur at lower chemical pressures than required for the formation of the initial nucleus. Renal tubular cell injury can promote crystallization of CaOx crystals by providing substances for their heterogeneous nucleation. *In vitro* cell degradation following renal tubular cell injury produces numerous membrane vesicles, which have been shown to be good nucleators of calcium crystals. *In vivo* crystals observed in the renal tubules of hyperoxaluric rats are always associated with cellular degradation products (Fasano and Khan, 2001; Khan *et al*., 1990).

Crystal growth: Once a crystal nucleus has achieved a critical size and relative supersaturation remains above one, the overall free energy is decreased by adding new crystal components to the nucleus. This process is called crystal growth. Crystal growth is one of the prerequisites for particle formation and thus for stone formation (Finlayson *et al*., 1983).

Crystal aggregation: The process by which crystals in solution (urine) stick together to form larger particles is called aggregation (Sakhaee, 2009b). Some researchers have proposed that crystal aggregation is the most important step in stone formation. Although, crystal growth is an important step in CaOx stone formation, the process of growth is so slow that crystals cannot become large enough to obstruct the renal tubules and be retained there by this mechanism alone. For this reason, the more critical step is thought to be crystal aggregation (Kok and Khan, 1994). All models of CaOx urolithiasis concede that crystal aggregation is probably involved in crystal retention within the kidneys, since aggregation of crystals can have a considerable effect on particle size and aggregated crystals are commonly found in urine and renal stones (Kok and Khan, 1994). Crystal aggregation is promoted by viscous binding molecules or cementing substances present in matrix.

Matrix components: The matrix is an important component of urolith consisting of various macromolecules consisting of lipids and proteins. Phospholipids account for approximately 10.25% of stone matrix (Khan *et al*., 1988). Various identified phospholipids and glycolipids include sphingomyelin, phosphatidylcholine, phosphatidylethanolamine, cardiolipin and trace amounts of phosphatidylserine in all stone matrices (Khan *et al*., 2002). In all stones, glycolipids include gangliosides, sphingosine and glucocerebrosides. Lipids play a more active role since cell membranes and the lipids of CaOx stone matrix can catalyse the nucleation of CaOx from a metastable solution (Khan *et al*., 1996, 2002). Cell membranes and their lipids play critical roles in the process of calcification. Particular membrane phospholipids promote the formation of calcium oxalate and calcium phosphate and become a part of the organic matrix of growing calcification (Khan *et al*., 2002).

Protein plays an important component of matrix which may consists of various macromolecules like Tamm-Horsfall protein (Aggarwal *et al*., 2013), osteopontin (Lee *et al*., 2011),

sialic acid (Verkoelen and Verhulst, 2007), urinary prothrombin fragment 1 (Aggarwal *et al*., 2013), calgranulin (Pillay *et al*., 1998), albumin (Aggarwal *et al*., 2013), hyaluronic acid (Asselman *et al*., 2003), annexin II (Gerke and Moss, 2002), CD_{44} (Asselman *et al*., 2003), matrix Gla protein (Gao *et al*., 2007), monocyte chemo-attractant protein 1 (Kim and Tam, 2011) etc.

CLINICAL SIGNS

Clinical signs may be associated with partial or complete urethral occlusion. Animals with partial obstruction dribble blood-tinged urine after prolonged and painful attempts at urination. There is dysurea, hematurea, strangurea. Urine may also dry on the preputial hairs and leave detectable mineral deposits (Parrah *et al*., 2010). Animals with complete urethral obstruction exhibit tenesmus, tail twitching, weight shifting and signs consistent with colic (Loretti *et al*., 2003). Inappetance, bloat, depression and rectal prolapse also may be seen. Affected steers may elevate the tail and show urethral pulsations just ventral to the rectum. Goats may vocalize. Common sequel of complete urethral obstruction includes urethral perforation, hydronephrosis or urinary bladder rupture. Bladder rupture often results in death from uremia (Houston and Moore, 2009; Bartges *et al*., 2004).

RECENT ADVANCES IN MANAGEMENT AND TREATMENT OF UROLITHIASIS

In spite of substantial progress in the study of the biological and physical manifestation of urolithiasis, there is no satisfactory drug available for the treatment of urolithiasis, especially for the prevention of recurrence of the stones (Moe *et al*., 2011). At present time, conservative measures like increased fluid intake to ensure sufficient urinary dilution and conventional treatments including alkali therapy, thiazide diuretics and allopurinol are somewhat effective for various types of urolithiasis, but none of them are 100% effective (Sakhaee, 2009a). The agents used clinically for prophylactic therapy are primarily aimed to correct the underlying metabolic disorders but the evidence for their effectiveness is still not convincing in addition to their side effects and tolerability (Mattle and Hess, 2005). One reason for a limited success of chemical drugs in urolithiasis is that multiple factors are involved in its pathogenesis (Kmiecik *et al*., 1997) and thus treatment demands multiple targets, such as antispasmodic, antioxidant and anti-inflammatory activities (Khan *et al*., 2012b). Therefore, the present situation demands a newer approach of therapy.

Many allopathic agents like thiazide diuretics, alkali (potassium citrate), allopurinol, sodium cellulose phosphate, penicillamine (cuprimine), analgesics, bisphosphonates, potassium phosphate and probiotics (*Oxalobacter formigenes*) etc. are used in treating stones (Zerwekh *et al*., 2007; Coe *et al*., 2005; Hatch and Freel, 2005). Thiazide diuretics (e.g., hydrochlorothiazide, chlorthalidone and indapamide) produce an increase in tubular reabsorption of calcium, which diminishes hypercalciuria, and hence are effective in reducing calciuria and stone recurrence especially CaOx, $CaCO_3$ (Zillich *et al*., 2006). These drugs also induce positive calcium balance and thereby increase bone mineral density. Alkalis are used to increase the urinary citrate excretion in patients with hypocitriuria (Zerwekh *et al*., 2007). Allopurinols are used to reduce uric acid synthesis by blocking conversion of xanthine and hypoxanthine to uric acid. Thus reduce urinary excretion of uric acid in patients with hyperuricaemia and hyperuricosuria (Ngo and Assimos, 2007). Sodium Cellulose phosphates (SCP) are used to restore normal calcium excretion by reducing intestinal calcium absorption. Sodium Cellulose Phosphate may also induce hypermagnesiuria leading to increase saturation of CaOx by reducing the complex formation of urinary oxalate (Mikawlrawng and Kumar, 2014). Penicillamines are often recommended if drinking more fluids does not control cystine formations. Analgesics are recommended for less painful passage of ureteral stones which are expected to pass spontaneously. They are also useful in controlling recurrent pains associated with urolithiasis. Bisphosphonates are used to decrease calciuria. Potassium phosphates help in increasing serum phosphate, increase urine phosphate and possible increase in urine pyrophosphates. *Oxalobacter formigenes* and other probiotics help in decreasing oxalate excretion (Hatch and Freel, 2005). However, most of these standard pharmaceutical drugs used to prevent and cure urolithiasis are not effective in all cases, costly, quite common reoccurrences, risks of long term fertility, potential side effects and no guarantee (Mikawlrawng and Kumar, 2014).

Before the advent of lithotripsy and ureteroscopy, most patients with symptomatic upper tract calculi underwent open surgical lithotomy. However, lithotripsy and ureteroscopic extraction have dramatically reduced the role of open stone surgery (Matlaga and Assimos, 2002; Paik *et al*., 1998). Despite these advancements, techniques such as extracorporeal shock wave lithotripsy and percutaneous nephrostolithotomy do not assure the prevention of recurrence of the stone. They cause side effect such a haemorrhage, hypertension, tubular necrosis and subsequent fibrosis of the kidney leading to cell injury and ultimately

recurrence of renal stone formation (Terlecki and Triest, 2007). Also these methods are costly, non-affordable by the poor section and the re-occurrence rate is also high (50-80%) (Ziadi *et al*., 2006). Thus, even with the improved understanding of the mechanisms of stone formation and treatment, the worldwide incidence of urolithiasis is quite high and there is no truly satisfactory drug for treatment of renal calculi (Khan *et al*., 2012b).

ROLE OF MEDICINAL PLANTS IN TREATMENT OF UROLITHIASIS

Medicinal plants have been known for millennia and are highly esteemed all over the world as a rich source of therapeutic agents for prevention of diseases and ailments (Sharma *et al*., 2008). India is heritage of medicinal plants. There has been a growing interest in traditional herbal remedies due to its high margin of safety, cost effective, eco-friendly and readily availability (Jain, 2006). People living in the interiors and inaccessible remote rural areas have excellent knowledge about medicinal utility of the local flora. People in such areas have been traditionally using indigenous folk remedies to cure various diseases for generations and passing on this knowledge orally. Because of prompt and positive effect of herbal treatment they have strong faith in their own folk medicinal preparations or crude formulations (Purohit and Prajapati, 2003; Pifferi *et al*., 1999). A list of medicinal plants in treatment of urolithiasis and ailments related to urinary system has been reported by various researchers around India (Tiwari *et al*., 2012). Moreover, most of these medicinally claimed plants are yet to be validated scientifically and subjected to phytochemical analysis for their efficacy except a few of them.

Antiurolithiatic and renoprotective effect of various medicinal plants had been reviewed and reported by various researchers around the glove including India. A list of medicinal plants in treatment of urolithiasis and ailments related to urinary system has been depicted in Table 1. Tiwari *et al*. (2012) reported the antiurolithiatic and renoprotective effect of *Aerva lanata*, *Ammannia baccifera*, *Steracantha longifolia*, *Homonia riparia*, *Imperata cylindrica*, *Mimosa pudica* and *Rotula aquatic* at Manipal and Tirupati. Some of the plants showed promising results against magnesium ammonium phosphate and/or calcium oxalate type of stones. Ethanolic extract of *Ammania baccifera* was reported to be effective as prophylactic and curative against phosphate type of stones. Ethanolic extract of roots of *Homonia riparia* has effective prophylactic and curative activity against calcium oxalate and struvite stones. Ethyl acetate extract of *Rotula aquatica* showed significant antilithic activity against struvite stones and calcium oxalate stones. Phycocyanin a known antioxidant is reported to have potential antiurolithiatic activity as it reduces oxalate levels in kidney tissue significantly. 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

Table 1: List of medicinal plants commonly used as antiurolithiatic agents in India

Plants	Common names	Parts used	Uses	References
Abrus precatorius Linn. Chaning	Angouba	Leaves	Aqueous extract is used for treatment of kidney stones	Lokendrajit *et al*. (2011)
Allium odorosum Linn.	Yenam nakuppi	Leaves	Boil extract of leaves is given in painful urination especially urinary tract infections due to stone	Mikawlrawng and Kumar (2014)
Cinnamomum bejolghota (Buch-Ham.) Sweet.	Tezpat	Bark, leaves	Useful for treatment in urinary stone troubles	Alok *et al*. (2013)
Indigofera tinctoria Linn.	Neem	Roots	Roots are used in urinary complaints	Lokendrajit *et al*. (2011)
Momordica cochinchinensis (Lour.)	Karrot	Fruits	Kidney stone treatment	Prachi *et al*. (2009)
Tamarindus indica Linn.	Imli	Fruit	Boiled decoction of the leaves with sugar helps in exiting and eliminating calculi/stones	Lokendrajit *et al*. (2011)
Argemone mexicana	-	Root	Root powder is given for burning urination	Mikawlrawng and Kumar (2014)
Tribulus terrestis (L.)	Chota gokharu	Fruit	Used in treatment of kidney stone	Alok *et al*. (2013)
Tridex procumbens (L.)	-	Leaves	Leaf paste is given for kidney stone	Prachi *et al*. (2009)
Zea mays (L.)	Corn	Tassel	Given orally to expel the stone	Mikawlrawng and Kumar (2014)
Dolichos biflorus	Horse gram	Seeds	Diuretic, astringent, tonic, urolithiasis	Mikawlrawng and Kumar (2014)
Tinospora cordifolia (Wild) (L.)	Guduchi	Stem	Crushed stem to expel the stone	Ghatapanadi *et al*. (2010)
Curcuma longa	Haldi	Rhizome	Diuretic, choleretic, hepatoprotective	Mikawlrawng and Kumar (2014)
Aegle marmelose (L.)	Wood apple, bael	Leaves and fruit	Spoon of fruit pulp powder is taken orally with coconut milk for 14 days to dissolve kidney stones	Sharma *et al*. (2011)
Daucas carota (L.)	Wild carrot	Rhizome	One glass juice is given for night to remove kidney stone	Alok *et al*. (2013)

smooth musculature to cholinergic ligands (Prasad *et al*., 2007). Sayana *et al*. (2014) evaluate the antiurolithiatic activity of alcoholic extract of root of *Cissampelos pareira* in albino rats and found significant result in reduction of urinary stone formation as well as kidney function biochemical analysis and histopathological findings. Similar findings were also observed by taking lemon juice in rat model by Touhami *et al*. (2007).

Mikawlrawng and Kumar (2014) reviewed the effect of 107 medicinal plants belonging to 51 different families for the treatment of kidney stones and ailments related to urinary system in Manipur from 2005 till 2014. Dinesh *et al*. (2013) reported the 20 plants species belonging to 13 angiospermic families of which 4 species of plants from Amaranthaceae and 2 species each from Fabaceae, Malvaceae, Cucurbitaceae and Padaliaceae in treatment of kidney stone by native folklore of Nizamabad District, Andhra Pradesh, India. Pillai (1995) reported the antiurolithiatic efficacy of the core of the pseudostem of musa in human patients.

CONCLUSION

A urinary stone disease remains a major livestock health concern. With its multi factorial etiology, complex pathophysiology and high rate of reoccurrence it acts as a major constrain in animal husbandry practice. The complex pathophysiology of stone formation usually includes urinary supersaturation, crystal nucleation, precipitation, growth, aggregation of crystals and their retention in renal tubular epithelial cells. None of the conventional therapies are also 100% effective which are available for management of urolithiasis in animals. Medicinal plants had been used as an alternative therapy since Vedic era for both prevention and treatment of urinary stone diseases. Herbal medicines also possess high margin of safety, lesser side effect, eco-friendly, cost effective and more accessible by most of the animal owner. Hence, research on medicinal plants as anturolithiatic agents should be promoted.

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