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An overview of some promising medicinal plants with *in vitro* anti-urolithiatic activity

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Abstract : *Kidney stone formation is so acute in some places that they are called stone belts and Gujarat is one of them. Though most prevalent and widespread disease in the world, no guaranteed cure is found till date. None of the known and available treatments prevent the reoccurrence of kidney stone formation. Hence a dire need for herbal formulation appears to be the need of the hour. The present review discuses the causes, cure and treatment of kidney stone formation. It emphasizes herbal remedies and lists of some of the promising plants which show in vitro anti urolithiatic activity. They can be further taken up for in vivo studies or may be used in herbal formulations and find a new herbal drug to treat this dreadful diseases.*

Key words: *kidney stone, anti urolithiatic activity, in vitro, medicinal plants, herbal formulation*

I. INTRODUCTION

India has a great diversity of medicinal plants. There are thousands of plants which are used in traditional medicinal system to cure many diseases since thousands of years. They are one of the important sources of medicines known since ancient time for its medicinal properties. Medicinal plants as a group comprise approximately 8000 species and account for about 50% of all the higher flowering plant species in India. The knowledge of medicinal plants has been accumulated in the course of many centuries based on different medicinal systems such as Ayurveda, Unani and Siddha (Ragavendran, 2011). A large portion of the world population, especially in developing countries depends on the traditional system of medicine for a variety of disease (Sundaram *et al*., 2010). Herbs and spices have been used since antiquity for their flavoring qualities and also for their preservatives and medicinal properties. Their extracts have been used to cure various disorders, spasmodic gastric-intestinal complains, cough, bronchitis, laryngitis, tonsillitis and acting as carminative and diuretic agents. Therefore, the demands for these plants are increasing in both, industrialized and non- industrialized countries which leads to increase in their prices (Roby *et al*., 2013).

Urolithiasis, the word is derived from Greek word Ouron, "urine" Lithos, "stone". Urolithiasisis is the condition where urinary calculi are formed or located anywhere in the urinary system or the process of formation of the stone in kidney, bladder, and/or ureters (urinary tract) (Rajeshwari *et al*., 2013) (Fig. 1). It also occurs in Gall bladder (Fig. 2).

A large number of people, nearly 4-15% of the human populations suffer from urinary stone problem all over the globe (Khare *et al*., 2014). In India, the "stones belt" occupies, parts of Maharashtra, Gujarat, Punjab, Haryana, Delhi and Rajasthan. South has less prevalence. In India, 12% of the population is expected to have urinary stones, out of which 50% may end up with loss of kidneys or renal damage. Since urolithiasis is a multidactorial disease, its etiology is very complex and highly unpredictable (Yashir and Waqar, 2011).

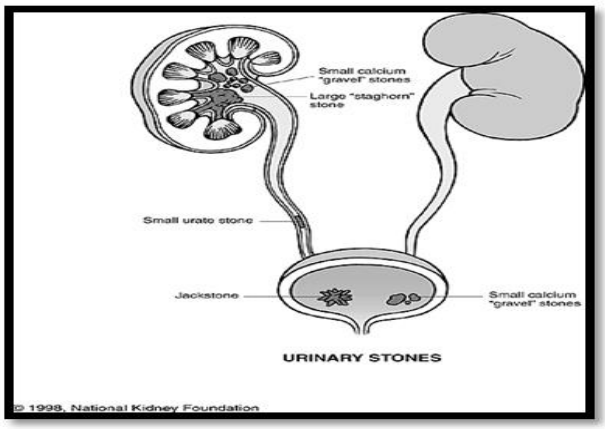


Fig. 1 Stone in urinary tract

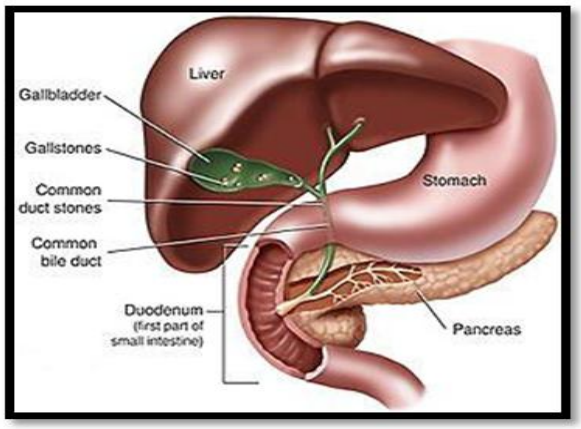


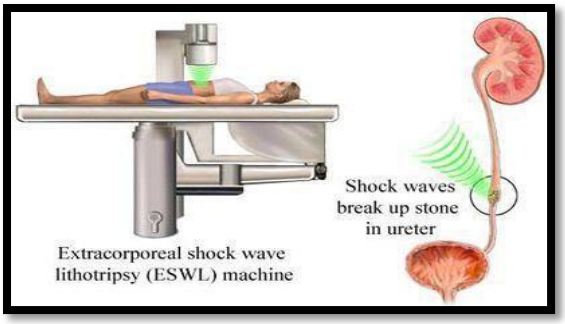
Fig. 2 Stone in gall bladder

The occurrence of kidney stone formation in some areas is so acute and alarming that they are called "stone belts". Gujarat is called the "Stone Belt". Kidney stones are common among people from Saurashtra and North Gujarat due to high level of total dissolved salts (TDS) in water. Thus, North Gujarat and Saurashtra region in Gujarat has higher prevalence of urinary stones. A stone is an aggregation of solute materials from urine such as calcium, oxalate, phosphate and uric acid which forms stone. In India, calcium oxalate is found to be the most predominant constituent of urolithiasis (Agarwal *et al*., 2014).

Calcium oxalate stones represent up to 80% of analyzed stones (Awari *et al*., 2009). Calcium phosphate account for 15-25%, while 10- 15% is mixed stones. The others are struvite 15-30%, cystine 6-10%, and uric acid stones 2-10% (Shashi *et al*., 2013). Calcium oxalate stones are of two types, calcium oxalate monohydrate (whewellite) and calcium oxalate dehydrate (weddellite). The occurrence frequency of whewellite is 78% while that of weddellite is 43% (Rao *et al*., 2011). Kidney stones are hard, solid particles and occur due to several factors like excess amount of stone forming constituents (calcium oxalate, calcium phosphate, uric acid struvite and cystine), imbalance between promoters (e.g. sodium urateset) and inhibitors like citrate, glycosaminoglycans, etc. (Evan *et al*., 2003). There are different sizes of stones. In many cases, the stone are very small and can pass out of the body without any problems. However, if a stone blocks the flow of urine, excruciating pain occurs and prompt medicinal treatment is needed (Atodariya *et al*., 2013).

When the stone forming constituents are excess in urine it become supersaturated, leads to the precipitation and finally it grows as stone. The biochemical process involved in calcium oxalate stone formation is super-saturation, nucleation, aggregation, crystal growth, crystal retention and formation of stone nidus and finally development of stone (Joshi *et al*., 2012). Medical conditions that are associated with increased risk of kidney stone formation include hyperparathyroidism, hyperthyroidism, gout, cystic fibrosis (Kramer *et al*., 2003). Symptoms for urolithiasis include abnormal urine colour, blood in urine, fever, nausea and vomiting (Louis and Liou, 2009). Physicians usually do not treat kidney stones; they just medicate the pain until the stone pass out on their own. Vegetarian diet, heavy on herbs and liquids, can be helpful in the prevention and treatment of kidney stones. So the best way to prevent kidney stone is to drink plenty of water and take a vegetarian diet high in magnesium (Tiwari *et al*., 2012).

Management of stone diseases depend on the size and location of the stones. Stone larger than 5mm or stones failed to pass through should be treated by some interventional procedures such as Extracorporial Shock Wave Lithotripsy (ESWL) (Fig. 3), Ureteroscopy (URS) or Percutaneous nephrolithotomy (PNL) (Fig. 4) (Coll *et al*., 2002). All these treatment options are, for stones found anywhere in the urinary tract but unfortunately there is no treatment option for the stones found in gall bladder; the only option being removal of gall bladder.



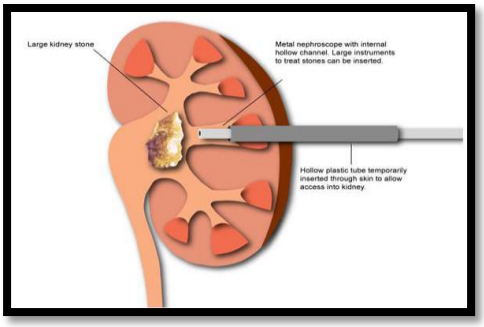


Fig. 3 Extra corporeal shockwave lithotripsy **Fig. 4 Percutanious nephrolithotomy**

Unfortunately, the propensity for stone recurrence is not altered by removal of stones with ESWL and stone recurrence is still 50% (Nobi *et al*., 2007). In addition, ESWL might show some significant side effects such as renal damage, ESWL induced hypertension or renal impairment (Tombolini *et al*., 2000). However, these treatment options are costly and recurrence is quite common.

Many medicines like Thiazide diuretics (e.g. Hydrochlorothaizide), alkali, (e.g. Potassium citrate), Allopurinol, Sodium Cellulose Phosphate (SCP), Penicillamine (Cuprimine), Analgesic (Diclophenac sodium), Bisphosphonates, Potassim phosphate, Oxalobacter Formigenes and other probiotics are used in treating the stones formed which act by decreasing the excretion of stone forming agent such as oxalates, calcium, phosphates, etc (Choubey *et al*., 2010).

Now-a-days, however, herbal medicine has gained much popularity because, herbal medicines are more effective, have less side effects and reduce recurrence rate of stone formation, hence search for antilithiatic drug from natural sources has assumed greater importance and is promising. In Ayurvrda, many plants having the property of disintegrating and dissolving the stone are referred to as "Pashanbheda" (Agarwal and Varma, 2014). Herbal medicines have many phytoconstituents which may exert their beneficial effect in kidney stone treatment. Plant extracts contain phytochemicals that inhibit stone formation by inhibiting synthesis and agglomeration of crystals (Bhattacharjee *et al*., 2012).

Herbal extracts may prevent stone formation because of many reasons like they may have diuretic activity, crystallization inhibiting activity, lithotriptic activity, analgesic and anti-inflammatory activity (Joy *et al*., 2012). And finally regulate oxalate metabolism which help in reducing the reoccurrence of renal calculi (Pareta *et al*., 2011). There are some general measures of prevention of kidney stone formation. For e.g. increase in fluid intake, decrease in take of animal protein like meat, eggs and fish contain purines that can increase the risk of uric acid stones and calcium stone formation. Lemonade and citrus drinks are helpful in reducing the problem of stone formation as the juices contain citrates which control growth of crystals to form stones. But the intake of juices like grape fruit juice, cranberry juice and dark colas may increase the risk of stone formation as these contain oxalates (Joy *et al*., 2012).

Herbal remedies are reported to be effective with no side effects. The drug for prevention of the disease or its re-occurrence is of great concern as no drug in clinical therapy is of satisfactory result (Sundararajan *et al*., 2006) (Fig. 5).

Fig. 5 Herbal remedies

Urolithiais is a largely recurrent disease with a relapse rate of 50% in 5-10 years. Studies include that 1 in every 1000 people pass a calcium oxalate calculus each year. It is also characterized by a high rate of recurrence which is reported to range from 40% within 3 years of the first incidence of kidney stones. (Yasir and Waqar, 2011). Stone formation is culmination of a series of physicochemical events i.e. super-saturation, nucleation, growth of the crystal and aggregation that occurs as the glomerular filtrate traverses through the tubules of nephron. Urine is normally supersaturated with most stone forming salt components, as well as contains chemicals that prevent or inhibit crystal development in urinary tract. However, the presence of super-saturation of salts needed to initiate crystal nucleation or reduce the rate of crystal growth or crystal aggregation and prevent stone formation.

Recently significant progress has been made in identifying and quantitating physicochemical processes responsible for urinary stone formation. It was shown that the urine of normal people and stone-formers had a similar level of super-saturation. It is evident that super-saturation of urine with calcium oxalate is essential for urinary calcium oxalate crystallization (Kulaksizogu *et al*., 2008). Though technological advancement have made dramatic improvement in the removal of urinary stone still some of the drawbacks of these methods exists which include their being too costly for a common man and recurrence of stone formation along with the number of other side effects (Prasad *et al*., 2007). Urolithiasis is a major problem affecting many people since ages. The main cause of stone formation is calcium oxalate and calcium phosphate accumulation. The stages involved in the accumulation of these two substances include: nucleation, crystal growth, crystal aggregation and crystal retention. Nucleation occurs because of super saturation and this is the first step in the formation of a renal stone in the form of a solid crystal.

The best way to prevent and treat urolithiasis is to control the process of crystallization events and most important step is to control the initial step i.e. nucleation step. This is best achieved by the use of herbal extracts since they have been widely used in folk medicine to treat kidney stones. The idea to use herbal extracts in the first step is that if nucleation itself is stopped or controlled, the next steps which lead to formation, aggregation and retention of crystals do not occur at all.In the present review, some promising plants showing antiurolithiatic activity as evidenced by *in vivo* studies and some plants which showed promising results in *in vitro* studies are reported (Table 1). In future, the *in vitro* studies can be further taken up for *in vivo* studies or the reported plant extracts can be used in formulation studies and find a new herbal drug to treat this ghastly diseases which till date has no cure. The table also describes the part and the solvent extract used. Such *in vitro* studies forms the basis and helps the researcher to work on a particular plant rather than random selection of the plant. Sofia et al., (2015) also reported some promising plants of antiurolithiatic activity.

However, further research is needed to identify the active principles from medicinal plants to assess their dosage and quality control and investigate their interactions and adverse effects. Many herbs themselves possess inhibitory activity against crystallization. The anti oxidant activity of the herbs also help in preventing the urolithiatic renal cell damage. Although use of herbal medicine is popular and promising, it is essential to carry out further research to understand the pathophysiology of disease, mechanism of action of herbal medicines inorder to develop an efficient and safe litholytic agent.

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Table 1: List of some medicinal plants, part used, solvent extracts and assays of antiurolithiatic activity

No.	Botanical name	Part used	solvent Extracts	Assays	References
1	Bergenia ligulata (Wall.) Engl.	Rhizome	ME, AQ	Turbidity	Bashir and Gilani, 2009
2	Beta vulgaris L.	Root	AQ	Nucleation aggregation and growth	Saranya and Geetha, 2014
3	Boerhaavia diffusa Linn.	Root	AQ	Ethylene glycol induced hyperoxaluria	Pareta et al., 2010
4	Boerhavia diffusa Linn. and Bryophyllum pinnatum (Lam.) Oken	Whole plant	ET	Crystallization assay	Yasir and Waqar, 2011
5	Ceropegia bulbosa Var. Lushii	Root	HE, ET, AQ	Titrimetric	Monica et al., 2012
6	Citrus limon (L.) Burm. f. and Citrus sinensis L.	Fruit	Juice	Nucleation and aggregation	Kulaksizoglu et al., 2008
7	Convolvulus arvensis L.	Leaves and flowers	AQ	Inhibition, kinetic study, nucleation, aggregation	Rajeshwari et al., 2013
8	Costus arabicus L.	Aerial parts	AQ	Crystallization assay	De Cogain et al., 2015
9	Dolichos biflorus Linn.	Seed	CHL, AQ	Supersaturation, nucleation, growth, aggregation and retention	Atodariya et al., 2013
10	Glochidion velutinum (Wight & Arn.)	Leaves	ME	Ethylene glycol induced hyperoxaluria	Vijaya et al., 2013
11	Hyptis suaveolens (L.) POIT.	Aerial parts	ET	Titrimetric	Agarwal and Varma, 2012
12	Kalanchoe pinnata Adans.	Leaves	AQ	Nucleation and aggregation	Phatak and Hendre, 2015
13	Lantana camara Linn.	Leaves	ET	Ethylene glycol and Ammonium chloride induced	Reddy, 2013
14	Launaea procumbens Linn.	leaf	ME	Ethylene glycol induced urolithiasis	Makasana et al., 2014
15	Melia Azadirachta L.	Aerial part	AQ	Zinc disc implantation	Hwisa et al., 2014
16	Melia dubai Cav.	Leaves	ET, AQ, AC	Turbidity	Vennila and Mariyal, 2015
17	Mimusops elengi L.	Bark	PE, ET, CHL	Ethylene glycol induced urolithiasis	Ashok et al., 2010
18	Moringa oleifera Lam.	Bark	AQ	Zinc disc foreign body insertion	Fahad et al., 2010
19	Ocimum gratissimum L.	Leaves	ET	Nucleation and synthetic urine	Agarwal and Warma, 2014
20	Pinus eldarica Medw.	Fruit	AQ	Ethylene glycol induced hyperoxaluria	Hosseinzadeh et al., 2010
21	Phylanthus niruri Linn.	Leaves	PE, EA, ME	Turbidity	Khare et al., 2014
22	Rotula aquatica Lour.	Leaves, Stem, Root	PE, CHL, ME, AQ	Nucleation and aggregation	Sasikala et al., 2013
23	Tamarix gallica L.	Leaves	DIE	Turbidimetric	Bensatal and Ouahrani, 2008
24	Terminalia chebula Retz.	Fruit	AQ	Ethylene glycol induced urolithiasis	Pawar et al., 2012
25	Tribulus terrestris Linn. Asteracantha longifolia Ness., Asparagus racemosus Willd, Mucuna pruriens Baker, Sida cordata (Burm. f.), Abutilon indicum Linn.	Gokhsuradi churan	AQ	Nucleation and synthetic urine	Srinivasa et al., 2013

(**Solvents:**- ME (Methanol); AQ (Aqueous); ET (Ethanol); HE (Hexane); CHL (Chloroform); DIE (Diethyl ether); EA (Ethyl acetate); PE (Petrolium ether)

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