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Review article

A BRIEF REVIEW ON THE POTENTIAL MEDICINAL PLANTS AND SCREENING MODELS OF UROLITHIASIS

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ABSTRACT: Kidney stones or urolithiasis is a growing global problem. It is a complex phenomenon which results due to physiochemical changes including super saturation, crystallization and retention within the renal tubules. The problem of the stone formation is considered as a medical challenge due to its high rate of recurrence and also due to multifactorial etiology. Medicinal plants are found to be useful in this metabolic disorder from ancient days due to its no or low-toxic nature, easily available in rural areas, cheap, there are less chances of recurrence. The purpose of this paper is to critically review available literature on herbal medicines and screening models for urolithiasis inorder to develop effective drug to treat the disease.

Keywords: Urolithiasis, Calcium oxalate crystals, Herbal medicines, screening models.

INTRODUCTION

Urolithiasis or nephrolithiasis are the oldest and wide spread painful urological disorders (Gilhotra.U.K, Christina.A.J.M, 2011). It is the third most prevalent disorder in urinary system (Vijaya.T, et al., 2013).

Urolithiasis / nephrolithiasis are commonly referred as stone formation in any part of the urinary tract such as kidneys, ureters, urinary bladder and urethra (Vidhya.G, et al., 2013). Urinary stones are generally caused by bacterial infection while kidney stones form as a result of physicochemical or genetic derangements leading to supersaturation of the urine with stone-forming salts or, less commonly, from recurrent urinary tract infection with urease producing bacteria like Proteus vulgaris, Pseudomonas aeruginosa, Enterobacter spp., Serratia spp., Staphylococcus aureus, Staphylococcus epidermitis (Alok.S, et al .,2013). Stone formation is a complex process which occurs due to the successive physiochemical events such as super saturation, nucleation, growth, aggregation and retention within the renal tubules (Yadav.R.D, et al., 2011).

Calculi can be broadly classified into two large groups:

1) Tissue attached: Attached calculi are mainly integrated by calcium oxalate monohydrate (COM) renal calculi, with a detectable attachment site to the renal papilla and basically consisting of a core located near to the attachment site (concave zone) and radially striated concentrically laminated peripheral layers.
2) Unattached calculi: Unattached calculi, with no detectable site of attachment to papilla, are developed in renal cavities of low or reduced urodynamic efficacy and can exhibit diverse composition and structures (Tiwari.A, et al.,2012).

It is a consequence caused due to an imbalance between promoters and inhibitors of crystallization in urine (Tiwari,.A et al., 2012).

Table 1: Stone promoter and inhibitors

Promoters	Inhibitors
Low urine volume	Inorganic inhibitors
Low urine pH	Citrate
Calcium	Magnesium
Sodium	Organic inhibitors
Oxalate	Prothombin fragment
Urate	Glycosaminoglycans
	Osteopontin

Of the total global population, urolithiasis occurs approximately about 12 % and it is estimated at 1-5% Asia, 5-9% Europe, 13% North America (Abbagani.S, et al., 2010). Approximately 7, 50,000 cases per year appear in Germany (Thomas knoll, 2010). In India, 12 % of the populations are expected to have urolithiasis and also nearly 15% of the population of North India suffers from kidney stones (Abbagani.S, et al., 2010). It is a male predominant disorder where the epidemiological data revealed that it occurs at a ratio of 2:1 /3:1 i.e., it occurs 12 % in men and 6 % in women between the ages 20 to 40 in both sexes with recurrence 70-81 % in males and 47-60 % in females (Sathish.R, et al.,2010) with a span of 20 years. Paedriatric nephrolithiasis have also been reported. The report rate of stone disease in children is predictable to 0.13 to 0.94 cases per 1000 hospitals occurring twice as commonly seen in boys than girls. Infected urolithiasis is more frequently seen in children younger than 4 years (Ankur.C, et al., 2010).
Urolithiasis is a common condition with multifactorial etiology. Many epidemiological factors, biochemical and genetic factor which includes age , sex, hereditary, occupation, bodysize, social class, affluence, geographic location, climate, diet, fluid intake and other medical conditions like hypertension, CVD, gout, cystinuria, hyperparathyroidism etc. predispose to stone disease (Abbagani.S, et al., 2010).
Urinary calculi may cause obstruction, hydronephrosis, infection, hemorrhage.

Table 2: List of plants used in the treatment of urolithiasis

S.No	Scientific name	Common name	Family	Plant part used	Reference
1	*Alhagi mannifera*	Camels Thorn	Fabaceae	Roots	Joy. J M, et al., 2012
2	*Apium graveolens*	Lavender	Apiaceae	Flowers	Alok.S, et al., 2013
3	*Barbarea vulgaris*	Rocket	Brassicaceae	Roots, Leaves	Ankur.C, et al.,2010
4	*Berginia ligulata*	Pasanabheda	Saxifragaceae	Rhizome	Tiwari. A, et al., 2012
5	*Boerhavvia diffusa*	Punarnava, Hogweed	Nyctaginaceae	Root	Pareta.S.K, et al.,2011
6	*Bridolia montana*	Chikitsa silianam	Euphorbiaceae	Bark	Alok.S, et al.,2013
7	*Bryophyllum pinnatum*	Patharchata, Ajubu, Ghavapatta, Parnbeeja	Crassulaceae	Fresh leaf juice	Ahmed. A, et al., 2013
8	*Capsella bursapastor L. Medik*	Mothers heart	Brassicaceae	Entire herb	Joy. J.M., et al., 2012
9	*Carica papaya*	Papaya	Caricaeae	Root, Fruit	Velmurugan. C, et al., 2013
10	*Celiosa argentea*	Plumed cockscomb, Feathery amaranth	Amaranthaceae	Roots	Kachchhi.N.R, et al .,2012
11	*Centratherum antehlminticum*	Van jeeraka, tikta jeeraka, kali jeeraka, aranya jeeraka	Asteraceae	Seeds	Ashok.P, et al .,2013
12	*Citrus medica Linn*	Bijoru	Rutaceae	Unripe fruits	Chavada Kalpeshsinh.S, et al., 2012
13	*Coleus aromaticus*	Country borage	Lamiaceae	Leaves	Venkatesh.G, et al., 2010
14	*Costus spiralis Roscoe*	Cana-do-brejo, Cana-de-macaco	Zingiberaceae	Whole plant	Joy.J.M, et al .,2012
15	*Crateva magna Lour.*	Barna	Capparidaceae	Bark	Mekap.S.K, et al .,2011
16	*Cucumis sativus*	Cucu, Cucumber	Cucurbitaceae	Leaves	Ankur.C, et al.,2010
17	*Cucumis trigonus R.*	Kattutumatti	Cucurbitaceae	Fruit	Balakrishnan.A, et al., 2012
18	*Curculigo orchioides*	Kali musli, Golden eye grass	Amaryllidaceae	Root	Ratnam .K.V,et al., 2013

19	*Desmodium styracifolium*	Korat nasi	Leguminosae	Whole plant	Joy.J.M, et al., 2012
20	*Didymocarpus pedicillata*	Stone flower, Shantapushpi, Charela, Patharphori	Gesneriaceae	Leaves	Alok.S, et al., 2012
21	*Dolichops biflorus*	Kulattha, Horsegram, Ulavalu	Fabaceae (Papillionaceae)	Seeds	Alok.S, et al., 2012
22	*Equisetum debile (Roxb))*	Jod tod ki ghas		All parts	Sharma.N, et al., 2011
23	*Glochidion velutinium*	-	Euphorbiaceae	Dried leaves	Vijaya.T, et al., 2013
24	*Gomphrena celosioides*	Gomphrena weed	Amaranthaceae	Whole plant	Sharma.N, et al., 2011
25	*Grewia flavescens*	Kali-siali	Tiliaceae	Root	Sharma.N, et al.,2011
26	*Herniaria hirsute*	Hairy rupture wort	Illecebraceae	Whole plant	Yadav.R.D, et al., 2011
27	*Hygrophila spinosa*	Gokulakanta	Acanthaceae	Whole plant , leaves	Satish et al 2010
28	*Jasminum auriculatum*	Usimalligai	Oleaceae	Flowers	Ankur.C et al., 2010
29	*Kalanchoe pinnata pers.*	Patharchatta	Crassulaceae	Leaves	Gilhotra. U. K, Christina A. J. M, 2011
30	*Lagenaria siceraria*	Bottle gourd, Calabash, Lauki, Dudhi	Cucurbitaceae	Fruit	Takawale.R.V, et al., 2012
31	*Macrotyloma uniflorum lam*	Madras bean	Fabaceae	Seeds	Joy.J.M, et al., 2012
32	*Mimosa pudica*	Touch-me-not	Mimosaceae	Leaves	Alok.S, et al., 2013
33	*Mimusops elengi*	Spanish cherry, Bullet wood	Sapotaceae	Bark	Ashok.P, et al., 2011
34	*Momordica charantia*	Bitter gourd, Carilla, Blasam peer	Cucurbitaceae	Fruits	Shah.B.N, et al., 2011
35	*Moringa oleifera*	Drum stick tree, Horse Radish tree	Moringaceae	Pods, Bark,Root, Wood	Joy.J.M, et al., 2012
36	*Musa paradisica*	Banana	Musaceae	Stem juice	Joy. J.M, et al., 2012
37	*Nardostachys jatamansi D C*	Spikenard, Musk-root, Sadamanchil	Valerianaceae	Rhizomes	Vidhya .G, et al., 2013
38	*Nigella sativa*	Black cumin, Small fennel	Ranunculacea	Seeds	Butterweck .V, Khan.S, 2009
39	*Pergularia daemia*	Pergularia, Dustapuchettu, Jittupaku	Asclepiadaceae	Whole plant	Vyas.B. A, et al., 2011
40	*Cassia fistula*	Indian Laburnum, Golden shower, Purging cassia	Caesalpiniaceae	Wood bark	Ramesh.C, et al., 2010

41	*Phyllanthus niruri*	Stone breaker	Euphorbiaceae	Whole plant	Yadav.R.D, et al.,2011
42	*Rosamarinus officinalis*	Rosemary	Lamiaceae	Leaves	Ankur.C, et al., 2010
43	*Rotula aquatic*	Pashanabedha	Boraginaceae	Roots	Joy. J.M, et al., 2012
44	*Rubia cordifolia*	Madder, Indian Madder	Rubiaceae	Root	Kalyani Divakar.A.T, et al.,2010
45	*Saccharum spontaneum*	Kasa	Solanaceae	Root	Sathya. M, et al., 2012
46	*Solanum surattence*	Yellow-berried nightshade	Solanaceae	Roots	Alok.S, et al., 2013
47	*Swertia chirata*	Chiretta	Gentianaceae	Stems	Parmar. R.K et al., 2013
48	*Terminalia arjuna Roxb*	Arjuna, Arjun tree	Combrataceae	Bark	Joy.J.M, et al., 2012
49	*Tinospora cordiofolia*	Guduchi, Giloy	Menispermaceae	Stems	Kumar.G.P, et al., 2011
50	*Origanum vulgare*	Marzanjosh, Wild Morjorum	Labitae/Lamiaceae	Whole plant	Khan.A, et al.,2011

Among the several types of kidney stones, the most common are calcium oxalate stones representing up to 75-90% of the analyzed stones, uric acid crystals accounts to 3-10%, the struvite (Magnesium ammonium phosphate) is of 10-15% and cystine stones 0.5-1% (Joy.J.M, et al., 2012). Management of stone disease depends on the size and location of the stones. However, size and location of the calculi play an important role in predicting spontaneous passage. In several studies, it was reported that spontaneous passage rate of urinary stones ranges between 70-98 % for small ($\leq$ 5 mm) distal ureteric calculi. Large calculi (stones larger than 5 mm) associated with unbearable pain or stones that fail to pass through should be treated by some interventional procedures like extracorporeal shock wave lithotripsy (ESWL), uteroscopy (URS), percutaneous nephro lithotomy (PNL) and surgery (Mohanty.N.K,et al .,2010). These procedures are costly, risky, recurrence is common, and also show several adverse effects like hypertension, trauma, hemorrhage, renal impairement etc.

Various therapeutic strategies are also available which includes diet management (increased fluid intake, restriction of oxalate rich food like spinach, reduced intake of vit.C and D) ; diuretics (hydrochlorothiazide, indapamide) ; expulsion therapy (calcium channel blockers, steroids, NSAIDS, alpha 1 –adrenergic receptor antagonists) ; chelating agents (magnesium, citrate, magnesium citrate) and probiotic therapy have been used either alone or in combination to have effective treatment against urolithiasis. However they have their own pharmacological limitations and no.of side effects and moreover the scientific evidence for their efficacy is less convincing and there is still no satisfactory drug to use in clinical therapy for prevention of the recurrence of stones (Chavada Kalpeshsinh.S, et al., 2012).

The problem of the stone formation is considered as a medical challenge due to its high rate of recurrence and also due to multifactorial etiology. From the earlier studies and literature of review it was proved that phytotherapy has a promising role in the prevention and cure of renal calculi with fewer side effects and low rate of recurrence. Hence for the development of highly effective, safe and least expensive drug there is a need of the study of the animal models of urolithiasis resembling in humans.

SCREENING METHODS OF UROLITHIASIS

I) Preclinical animal models of urolithiasis

1) Ethylene glycol induced urolithiasis in rats

Chemically ethylene glycol is ethan-di-ol and is widely used as a solvent and automobile antifreeze agent (Saha. S, Verma.R.J, 2012).

Mechanism of action

Ethylene glycol is rapidly absorbed and metabolized in liver via alcohol dehydrogenase and aldehyde dehydrogenase to glycolic acid. This is oxidized to glyoxylic acid which is further oxidised to oxalic acid/oxalate by glycolate oxidase / lactate dehydrogenase, thus promoting hyperoxaluria. Hyperoxaluria is the major risk factor for urolithiasis. Dose: 0.75% v/v in drinking water for 28 days.

Method

Healthy male wistar rats (120-200gm) are taken. They are divided into four (4) groups each group containing 6 animals. Group-I served as control and given vehicle for 28 days. Group –II, III, IV served as positive control, standard and test groups and were given ethylene glycol (0.75 % v/v, *p.o*) for 28 days. Group –III & IV are given standard drug cystone (750 mg/kg, *p.o*) and test drug respectively for 28 days. On the 28 th day urine and serum of all the animals are collected and all the required parameters are performed and compared (Shah. B.N, et al., 2011).

Advantages

1. It is widely acceptable model of urolithiasis for research as because, kidney being the most sensitive and principal target organ for ethylene glycol.
2. Ethylene glycol is widely available organic solvent.
3. Modulates oxalate metabolism (oxalate metabolism is similar both in humans and rats) and deposits micro crystals.

Disadvantages

1. Oxalate induced nephrotoxicity
2. Causes cellular damage

2) Diet induced model

Modified lithogenic diet consists of 30 % lactose rich diet and 1 % ethylene glycol. The 30 % lactose rich lab diet contains 3.68 % sucrose, 30 % lactose, 23.4 % protein, 10 % fat, 5.3 % crude fibre, 6.9 % ash minerals [Ca (0.95%); P (0.67%); Mg (0.21 %)], vit.A22 IU/g, vit D 4.5 IU/g, vit. E 49 IU/g.

Method

Healthy adult male wistar rats of 150-200 gm are procured and divided into four groups. Group I served as control and fed with regular lab diet. Group II, III, IV served as diseased control, standard and test respectively and they were given modified lithogenic diet (MLD) for 28 days. Simultaneously group III & IV are given standard drug and test drug resp. from day 1 to day 28 as preventive regimen. Various biological samples are collected, measured and compared.

Advantages of diet induced model

1. It is a non-nephrotoxic model of urolithiasis for research.
2. Diet induced urolithiasis is an effective model as it produces stable crystal deposition (Vidhya.G et al., 2012).

3) Induction of urolithiasis in rats by using sodium oxalate

Sodium oxalate induced urolithiasis is an acute model used to study the activity of urolithiasis caused by hyperoxaluria.

Dose: 70 mg/kg body wt

Route of administration: *i.p*

Treatment period: 7 days

Method

Healthy adult wistar rats (120-200 gm) were group obtained and randomly divided into four groups each group containing 6 rats. Group I as control , Group II, III and IV serves as positive control, standard and test groups resp. and injected with sodium oxalate 70 mg/kg , *i.p* for 7 days, simultaneously III and IV group were given standard drug cystone 750 mg/kg, *p.o* and test drug resp from day 1 to day 7 as preventive regimen. Various biological samples were withdrawn from each rat and compared to obtain results (Ramesh. C et al, 2010).

Advantages

1. It takes less time (short duration)
2. It is a reliable model and deposits microcrystals through a driving force hyperoxaluria as such ethylene glycol.

4) Zinc disc implantation induced urinary bladder calculi model

Male rats of wistar strain weighing 200-250 gm are used to study urinary calculi by zinc disc implantation. Rats were anaesthetized with sodium pentobarbitone (40 mg/ kg body wt, *i.p*). A suprapubic incision was made and urinary bladder was exposed. A small cut was made at the top of the bladder and a previously weighed sterile zinc disc (2 to 48 mg/kg) was inserted into the bladder and the incision was closed with a single suture using absorbable catgut. The abdomen was closed in layers and this was performed for each rat and all the rats are recovered for 1 week. At the end of 28 days treatment all the animals are measured for its different parameters and compared.

Advantages

1. This is a model that produces inflammation around the disc implanted area i.e., it actually causes attached calculi.
2. It is a non-nephrotoxic model.
3. It avoids the sacrifice of animals at the end of the study.

Disadvantages

1. It is a risky model.
2. It causes much more pain to the animal both due to insertion of disc and also because of surgery (Ahmad. A et al., 2013).

5) Xenoplantation model

Stone particles were extracted by PCNL (percutaneous lithotomy) from one male patient with renal stones. The selected stone is cut with a blunt instrument into sections with a diameter of 2-3 mm, weighed and maintained in a sterile environment, prior to use.

Eight week old male rats weighing about 250-300 gm were selected and randomized into 3 groups: control, standard and test groups. The rats were anesthetized by intraperitonel injection of sodium pentobarbital (50 mg/kg body weight) and the bladder was exposed by a suprapubic incision. Following this, a 4-5 mm incision was made at the top of bladder and one prepared stone particle was inserted in each rat and then the bladder and the suprapubic incision was closed respectively. Ethylene glycol was supplied in drinking water at a final concentration of 1 % from the second day (day 1) postoperatively for 4-weeks. After 4 weeks, kidney and urinary bladder were dissected and the kidneys were dehydrated in a graded ethanol series and embedded in paraffin. Renal stones formation was assessed by von Kossa histochemical staining. Bladder stones were harvested, weighed and maintained in 75% ethanol for 24 hrs, prior to the stones being embedded in auto-polymerizing resin and sectioned transversly with diamond wire saw inorder to select the best section pane. Sectioned blocks were then fixed on a glass slide with thermoplastic glue and polished successively using a 1, 200 grit sandpaper and a mix of alumina polishing compounds (3, 1 and 0.3 µm) with a small volume of water, until it was possible to observe the core clearly under a transmitted light microscope (Wang. S et al, 2013).

6) Chemically induced urolithiasis in weanling rats

Calculi is induced in the urinary tract of wealing Fischer-344 rats (postnatal day 28) in less than 2 weeks by exposure to terephthalic acid (TPA) at 3-5 % in the diet or dimethylterephthalate (DMT) at 1-3 % of diet. Specified rats of 24 which randomly divided into 4 groups each group containing 6 rats each. Group –I, II, III, and IV acts as control received vehicle, disease control (positive control) received (TPA) / (DMT) for 2 weeks, standard received (TPA/DMT) and cystone 750 mg/kg body weight *p.o* .and the last group i.e IV serves as test received (TPA/DMT) plus test drug.after the treatment period various biological samples are collected and the parameters are measured and compared (Wolkowski- Tyl.R et al., 1982).

Advantages

1. Wealing rats appeared to more susceptible to stone formation than adult rats.

7) Sulfamonomethoxine-Induced Urinary Calculi in Pigs

Five Yorkshine-Durox cross-bred castrated pigs within a farrow-to-finish herd with 346 commercial crossbred pigs weighting 45-60 kg were used. They are started on a regimen of SMM (50 mg/kg·BW) orally twice a day. The affected pig's medical history included streptococcal disease and toxoplasmosis, which were diagnosed in the third week and injected SMM (50 mg/kg·BW) once a day after toxoplasmosis was diagnosed (Wei-Dong.S et al., 2009).

8) Mild tubular damage for hyperoxaluric rats induces renal lithogenesis

It is a two step or two hit model of lithogenesis used to assess the anti-urolithiatic activity of test drugs. In the first step it is used to induce crystalluria (hyperoxaluria) which is necessary step but not sufficient to induce urolithiasis. In the second step it causes tubular damage that induces lithiasis (Gambaro.G, et al., 2006).

II. In-vitro model

In vitro crystallization

It is the time course measurement of turbidity changes due to the crystallization in artificial urine on addition of 0.01M sodium oxalate solution. The precipitation of calcium oxalate at 37°C and pH 6.8 has been studied by the measurement of turbidity at 620 nm using UV/Visible spectrophotometer.

Preparation of artificial urine:

sodium chloride 105.5 mmol/l, sodium phosphate 32.3 mmol/1, sodium citrate 3.21 mmol/l, magnesium sulfate 3.85 mmol/1, sodium sulfate 16.95 mmol/1, potassium chloride 63.7 mmol/1, calcium chloride 4.5 mmol/1, sodium oxalate 0.32 mmol/1, ammonium hydroxide 17.9 mmol/1, and ammonium chloride 0.0028mmol/1. The AU was prepared fresh each time and pH adjusted to 6.0.

Method:

Four test tubes was taken and transferred artificial urine of 1 ml into each tube and labeled as control (1), negative control (2), standard (3) and test (4).Test tube 1 &2 are added with 0.5 ml of distilled water, except test tube (1) all the test tubes are added with 0.5 ml of 0.05 M sodium oxalate and 3 & 4 test tubes are added with standard drug and test drug respectively. Test tubes are left to stand for 10 minutes. Immediately after 10 minutes the absorbance was measured in UV-Spectrophotometer at 620 nm and compared. Microscopy of urine can also be done using light microscope with objective of 40 X and eye piece of 10 X (Kumar. G. P et al., 2010).

CONCLUSION

As there is no proper medicine in allopathy for the management of urolithiasis and also the surgical treatment has the more chances of recurrence, these two factors particularly diverted the large population towards the use of herbal medicines. Medicinal plants has wide acceptance due to a large no. of advantages such as lesser toxic effects, safe, effective, cheap (cost effective), less chances of recurrence of disease,easily available in rural areas. The present paper provides information regarding the potential medicinal plants used in the management of urolithiasis and also about the screening models of urolithiasis inorder to develop a new drug for the management of urolithiasis to overcome the various disadvantages faced by the wide range of population now-a-days and get relieve from the disease. Let us hope for the development of safe and effective drug for the management of urolithiasis.

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