ANTI UROLITHIATIC HERBS AND EFFECTIVE SIDDHA FORMULATIONS

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ABSTRACT

The World Health Organization (WHO, 2002) emphasized development and utilization of herbal drugs and traditional medicines for the benefit of the world population in terms of cost effectiveness and low side effect. Plant medicines are in great demand both in the developed as well as developing countries for primary health care because of their wide range of biological and medicinal activities, higher safety margin and low cost. Many medicinal plants have been employed for centuries to treat urinary stones. The present review focus on the botanical information, Phytochemistry, Therapeutic uses, potential Pharmacological effect of some of the herbs, and Siddha formulations, being used in Siddha system of medicine for urolithiasis.

KEYWORDS: botanical information, Phytochemistry, Therapeutic uses, potential Pharmacological effect.

INTRODUCTION

Urinary stones have plagued human’s science the earlier records of civilization. A kidney stone is a hard mass developed from crystals that separate from urine and build up on the inner surfaces of the kidney. Urinary stones are polycrystalline aggregates composed of varying amounts of crystalloid and organic matrix. Crystal formation is modified by a variety of other substances found in the urinary tract, including magnesium, citrate, phosphate and a variety of trace metals. These inhibitors may act at the active crystal growth site or as inhibitors in solution (as with citrate). Calcium is a major ion present in urinary crystals.
Calcium nephrolithiasis is most commonly due to elevated urinary calcium, elevated urinary uric acid, elevated urinary oxalate or a decreased level of urinary citrate. Diuretic medications may exert a hypo calciuric effect by further decreasing calcium excretion. Uric acid stones comprise <5% of all urinary calculi and are usually found in men. Uric acid calculi can recur even more frequently. Dietary magnesium deficiency is associated with an increased incidence of urinary stone disease. Experimentally, lack of dietary magnesium is associated with increased calcium oxalate stone formation and calcium oxalate crystalluria.\textsuperscript{[1]}

Plants are superior sources of molecular diversity and novel molecular chemotypes. The plant kingdom represents a rich store house of organic compounds, many of which have been used for medicinal purposes. Traditional herbal medicine is now showing encouraging results and receiving recognition and respect. In recent years, search for plants having medicinal properties has got much impetus. Plants having medicinal value have been rediscovered and the search is still on at global level.\textsuperscript{[2]} This article is to focus the development of valuable phytomedicines from traditional medicinal plants in treating kidney stones. The present review incorporates 30 medicinal plants; few of a siddha formulations indicated for urolithiasis in ancient siddha literatures have potential antiurolithiatic activity in animal models and also clinically effective siddha drugs in the management of Urolithiasis.

1. \textit{Solanum xanthocarpum}

The isolated chemical constituents of Solanum xanthocarpum, Solasonine and Solasodine were found to have well anti urolithiatic and natriuretic activity having a negligible kaliuretic activity.\textsuperscript{[3]}

2. \textit{Pergularia daemia}

The alcoholic extract of the whole-plant, Pergularia daemia significantly (p<0.001) lowered the urinary excretion and kidney retention levels of oxalate, calcium and phosphate. Furthermore, high serum levels of urea nitrogen, creatinine and uric acid were significantly (p<0.001) reduced by the extract. The reduction of stone forming constituents in urine and their decreased kidney retention reduces the solubility product of crystallizing salts such as calcium oxalate and calcium phosphate which could contribute to the anti urolithiatic property of the extract. The extract exhibited significant diuretic activity at dose of 400mg/kg body weight as evidence by increased total urine volume and the urine concentration of Na\textsuperscript{+} and K\textsuperscript{+}.\textsuperscript{[4]}
3. Tribulus terrestris

The aqueous extract of Tribulus terrestris in oral dose of 5g/kg elicited a positive diuresis, which was slightly more than that of furosemide. The diuretic and contractile effect of Tribulus terrestris indicate that it has the potential of propelling urinary stones.\(^5\) Tribulus terrestris extract exhibited a concentration dependent inhibition of nucleation and the growth of CaOx crystals. When NRK-52E cells were injured by exposure to oxalate for 72 hours, Tribulus terrestris extract prevented the injury in a dose-dependent manner.\(^6\) In 0.2% ethylene glycol induced oxalate urolithiasis Wistar rats, the alcohol extracts of Tribulus terrestris, was found to be effective than spironolactone a potassium-sparing diuretic in reducing stone forming constituents both in urine and renal tissues and also reduced, the enzyme activity of GAO and LDH, out of this the alcohol extract of Tribulus terrestris was found to be more effective and highly significant in the reduction of calculi, which can be used as anti urolithiatic agent.\(^7\) Experimental studies carried out on Crataeva nurvala, Tribulus terrestris and Dolichos biflorus showed them to be effective in preventing the deposition of stone material on glass beads in the urinary bladder of rats.\(^8\) All the three plants were shown to dissolve phosphate type of calculi in an in vitro model, where as oxalate, uric acid and cystine stones were not dissolved by C. nurvala and D. biflorus extracts. T. terrestris dissolved uric acid and cystine stones to some extent. Clinical studies carried out on C. nurvala showed that it changes the urinary chemistry of patients and thus it reduces the Lithogenic potential.\(^9\)

4. Moringa oleifera

The effect of oral administration of aqueous and alcoholic extract of Moringa oleifera root-wood on calcium oxalate urolithiasis has been studied in Male Wistar albino rats. Ethylene glycol feeding resulted in hyperoxaluria as well as increased renal excretion of calcium and phosphate supplementation with aqueous and alcoholic extract of Moringa oleifera root-wood significantly reduced the elevated urinary oxalate showing a regulatory action on endogenous oxalate synthesis. The increased deposition of stone forming constituents in the kidneys of calculogenic rats was also significantly lowered by curative and preventive treatment using aqueous and alcoholic extracts. The results indicate that the root –wood of Moringa oleifera is endowed with antiurolithiatic activity.\(^10\)
5. **Momordia charantia**

Treatment with aqueous extract (200mg/kg,p.o) and alcoholic extract of fruits of Momordia charantia Linn. Significantly (p<0.001) lowered the increased levels of oxalate, calcium and phosphate in urine and also significantly (p<0.001) reduced their retention in kidney. The treatment with aqueous extract and alcoholic extract of fruits of Momordia charantia significantly (p<0.001) lowered the increased levels Blood urea nitrogen, creatinine and uric acid. The reduction in the stone forming constituents in urine and renal tissue brought about by Momordia charantia Linn. could contribute to its antiurolithiatic property.\[11\]

6. **Dolichos biflorus**

An aqueous extract of Dolichos biflorus at 10 mg concentration produces higher dissolution of calcium oxalate crystal by in vitro Anti-urolithiatic activity as compared to other fraction.\[12\]

7. **Raphanus sativus**

The aqueous extract of the bark of Raphanus sativus was tested for its antiurolithiatic and diuretic activity. The urolithiasis was experimentally induced by implantation of zinc disc in the urinary bladder of rats. Significant decrease in the weight of stones was observed after treatment in animals which received aqueous extract in comparison with control groups. This extract showed an increase in the 24hours urine volume as compared to the control.\[13\]

8. **Terminalia chebula**

The aqueous extract of the fruit of Terminalia chebula in wistar albino rats decreased the elevated levels of oxalate and phosphate in urine as well as kidney tissue homogenate. The extract supplementation also prevented the elevation of serum levels ie, Blood urea nitrogen, Creatinie and Uric acid.\[14\]

9. **Paronychia argentea**

The aqueous extract and Butanolic extract of aerial parts of Paronychia argentea prevent urinary stone retention by reducing renal necrosis and thus inhibit crystal retention.\[15\]

10. **Jasminum auriculatum**

Supplementation with aqueous and alcoholic extract of Jasminum auriculatum flowers significantly (p<0.001) lowered the elevated levels of oxalate, calcium and phosphate in
urine and kidney of ethylene glycol induced hyper oxaluria model in albino rats, compared to cystone treated animals.\textsuperscript{[16]}

11. Trigonella foenum graecum
The inhibitory effect of the aqueous extract of Trigonella foenum graecum seeds was examined on the formation of calcium oxalate renal stones induced by ethylene glycol with ammonium chloride. At the end of the experiment all kidneys were removed and examined microscopically for possible crystal/stone locations and the total calcium amount in the renal tissue was evaluated. The results showed that the amount of calcification in the kidneys and the total calcium amount of the renal tissue in rats treated with Trigonella foenum graecum was significantly reduced compared with the untreated group.\textsuperscript{[17]}

12. Pyrachantha crenulata
Alcohol extract of Pyrachantha crenulata fruit significantly (p<0.001) lowered the elevated levels of oxalate, calcium and phosphate in urine and kidney of ethylene glycol induced hyper oxaluria to male albino rats.\textsuperscript{[18]}

13. Benincasa hispida
Ethanolic extract of Benincasa hispida seeds significantly reduced the elevated urinary oxalate in 0.75% v/v Ethylene glycol induced hyper oxaluria in wistar albino rats showing regulatory action on endogenous oxalate synthesis and significantly lowered the urinary excretion and kidney retention levels of oxalate, protein and calcium. Moreover, elevated serum levels of sodium, creatinine and calcium, phosphorous were significantly reduced by the extracts.\textsuperscript{[19]}

14. Elettaria cardomomum
The inhibitory potency of different extracts of seeds of Elettaria cardomomum was evaluated on various stages of formation and on growth of calcium oxalate crystals. The alcoholic and aqueous extract has the higher capacity to inhibit the crystal formation and aggregation as compared to ethyl acetate and petroleum ether extracts.\textsuperscript{[20]}

15. Carica papaya
Aqueous and alcoholic extracts of the fruit of Carica papaya significantly (p<0.001) reduce the elevated urinary oxalate, showing a regulatory action on endogenous oxalate synthesis. The increased deposition of stone forming constituents in the kidneys of calculogenic rats
was also significantly lowered by curative and preventive treatment using aqueous and alcoholic extracts of the fruits of Carica papaya. Treatment with aqueous and alcoholic extracts of the fruits of Carica papaya significantly showed marked improvement in the damages caused by the ethylene glycol to the kidney and reduction in the crystal deposition.[21]

16. Asparagus racemosus
Ethylene glycol induced urolithiasis in Wistar albino rats treated with ethanolic extract of Asparagus racemosus significantly(p<0.05) reduced the serum concentrations of calcium, phosphorus, urea and creatinine and it elevated the urinary concentration of magnesium, which is considered as one of the inhibitors of crystallization.[22]

17. Cynodon dactylon
The ethanolic extract of Cynodon dactylon decreased the urine oxalate level in ethylene glycol induced urolithiasis in Wistar albino rats.[23]

18. Boerhaavia diffusa
The aqueous extract of Boerhaavia diffusa roots was found to possess a high total phenolic content and exhibited significant free radicals scavenging activity. Oxalate excretion significantly increased in hyperoxaluric animals as compared to control which was protected in Boerhaavia diffusa roots extract treated animals. Extract of Boerhaavia diffusa roots (BDE) treatment significantly reduced level of MDA and improved the activity of antioxidant enzymes followed by reduction in BUN and serum creatinine. In addition, BDE reduced the number of CaOx monohydrate crystals in the urine. Histological analysis depicted that extract of Boerhaavia diffusa roots (BDE) treatment inhibited deposition of CaOx crystal and renal cell damage.[24]

19. Coleus aromaticus
The urolithiatic rats treated with hydro alcoholic extract of Coleus aromaticus leaves (CALHAE) (300 and 600 mg/kg) have shown reduction in the number of calcium oxalate crystals in medulla region after 15 days treatment, as equiefficacious to cystone, treatment at 500 mg/kg dose level.[25]
20. **Mimusops elengi**
Alcohol extract of Mimusops elengi treated with ethylene glycol induced hyper oxaluria in male wistar albino rats significantly lowered the elevated levels of oxalate, calcium, and phosphate in urine and kidney thus reduces the risk of stone formation.\[^{26}\]

21. **Hordeum vulgare**
Administration of ethanolic excrac of Hordeum vulgare seeds on ethylene glycol induced urolithiasis in male wistar albino rats significantly reduced the urinary excretion of the calcium, phosphate, uric acid, magnesium, urea and oxalate.\[^{27}\]

22. **Punica Granatum**
The methanol extract and chloroform extract of Punica Granatum significantly decrease the urine oxalate, calcium and phosphate, renal tissue oxalates, serum creatinine, urea and uric acid in ethylene glycol induced urolithiasis in male wistar albino rats.\[^{28}\]

23. **Lawsonia inermis**
The hydro alcoholic extract of Lawsonia inermis leaves showed anti urolithiatic activity especially calcium oxalate type of stones in ethylene glycol with ammonium chloride induced kidney calculi in male wistar rats.\[^{29}\]

24. **Lagenaria siceraria**
Lagenaria siceraria fruit powder significantly reduces the elevated level of urinary oxalate, uric acid and creatinine on sodium oxalate induced urolithiasis in male wistar albino rats.\[^{30}\]

25. **Rubia cordifolia**
Hydro alcoholic extract of Rubia cordifolia significantly reduced the increase of oxalate in renal tissue and also the elevated calcium contents in ethylene glycol induced urolithiasis male rats. The number of calcium oxalate deposits in the tubules of hydro alcoholic extract of Rubia cordifolia treated rats was less.\[^{31}\]

26. **Phyllanthus niruri**
Phyllanthus niruri has an inhibitory effect on crystal growth, in a rat model of urolithiasis induced by introduction of calcium oxalate seed in bladder of rats. The effect may be due to higher Levels of glycosoamino glycans incorpated into calculi.\[^{32}\] *In vitro* studies in which calcium oxalate precipitation was induced by addition of 0.1 M sodium oxalate to unfiltered urine samples from Wistar rats and normal humans in absence and presence of Phyllanthus...
niruri extract (0.25 mg/ml), suggested that extract may interfere with early stages of stone formation.[33]

27. Crataeva nurvala
The effect of Crataeva nurvala bark decoction on calcium oxalate urolithiasis induced by 3% glycolic acid has been studied in rats. The decoction showed significant activity in preventing the deposition of calcium and oxalate in the kidney by inhibiting the activity of the Liver enzyme glycolic acid oxidase. Treatment with Crataeva nurvala bark decoction was reported to lower the levels of intestinal NaZ, KZ-ATPases.[34]

28. Aerva lanata
Administration of Aerva lanata aqueous suspension ((2g/kg body wt/day for 28 days) to CaOx urolithic rats had reduced the oxalate synthesizing enzymes, diminished the markers of crystal deposition in the kidney.[35]

29. Hypericum perforatum
Chronic administration of hydro alcoholic extract of Hypericum perforatum leaves (300 and 500mg/kg, orally) could significantly reduce the size and number of calcium oxalate deposits in Ethylene glycol induced kidney calculi in Wistar male rats.[36]

30. Nigella sativa
Administration of ethanolic extract of Nigella sativa (250 mg/kg, orally) reduced the number of calcium oxalate deposits and also lower the urine concentration of calcium oxalate in Ethylene glycol induced kidney calculi in Wistar male rats.[37]

Anti urolithiatic effect of Siddha formulations
1. Nerunjil kudineer
Urolithiasis was induced by 1% ethylene glycol administered in drinking water in Wistar strain female albino rats. Increase in serum urea was seen on day 14 and creatinine remained at the control value throughout the study. One group of ethylene glycol-treated rats received Nerunjil kudineer, a commercial Siddha drug containing powdered Tribulus terrestris, an indigenous plant. The drug-treated animals showed increased urinary output, decreased serum urea and crystalluria on day 14, and a tendency for alkalinization of urine compared with the ethylene glycol-treated animals, thus providing preliminary evidence for the clinical usefulness of this drug.[38]
2. **Vediuppu chunnam**

The efficacy of the two Siddha drugs, Aerva lanata and Vediuppu chunam as antilithic agents were studied in rats using 0.75% ethylene glycol in drinking water as a urolithic rat model. 650 mg – 1300 mg. Vediuppu chunnam (Sublimed form) along with Aerva lanata increases the urinary excretion of uric acid, calcium, oxalate, phosphorus and protein in hyperoxaluric rats and also decreases the magnesium excretion without adverse effects. The drug increases the urine volume, thereby reducing the solubility product with respect to calcium oxalate and other crystallizing salts such as uric acid, which may induce epitaxial deposition of calcium oxalate.

3. **Silasatthu parpam**

Karpoora silasathu act as a diuretic and Lithotriptic agent and is mainly indicated in the management of Renal calculi, Burning micturition and anuria. Magnesium present in *silasatthu parpam* increases the solubility of calcium oxalate and inhibits the precipitation of both calcium phosphate and calcium oxalate.

4. **Nandukkal parpam**

‘Nandukkal Parpam’ is used by Siddha practitioners for management of urolithiasis in human beings. The effect of oral administration of ‘Nandukkal parpam’ (a Siddha combination drug) on calcium oxalate microlithiasis was studied in male wistar rats. Ethylene glycol and ammonium chloride in drinking water were given orally to male wistar rats to induce calcium oxalate crystals in renal tissue the initial phase of urinary stone formation. The deposition of calcium oxalate crystals in kidneys of wistar rats on ethylene glycol and treated with Nandukal parpam is much lesser than in the group of rats on ethylene glycol only (p < 0.001).

**Clinical study of Siddha formulations in kalladaippu**

1. **Venkara parpam**

A clinical study of 30 renal calculi cases treated with 122 mg of venkara parpam with Raddish juice twice a day for 48 days. The stone was expelled in 3 cases. Calculi were completely dissolved in 12 patients. There is a significant difference between before and after treatment in the kidney stone size (p<0.02) and symptoms (p<0.0001).
2. **Kalladaippu thool**
A clinical study of 30 renal calculi cases treated with 5gm of Kalladaippu thool with Raddish juice twice a day for 8 weeks. The stone was expelled in 4 cases. Reduction of stone size and number of stones were observed in 9 cases. The USG report revealed that there is no evidence of stone in 9 cases.\[^{43}\]

3. **Karpoora silasatthu parpam**
An open clinical trial on Kalladaippu was conducted in NIS after obtaining approval of Institutional Ethics Committee (IEC- NIS/IEC/2011/03/04), which revealed that the mean standard deviation of renal calculi at before and after treatment were 8.30±3.16 and 4.2±4.03 respectively which is statistically significant (t=6.092 p<0.001) and the mean standard deviation of clinical symptoms score at before and after treatment were 4.95±1.89 and 2.93±0.66 respectively which is highly significant (t=7.5 p<0.0001).\[^{44}\]
Table: 1 Anti urolithiatic plant descriptions \[2, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54\]

<table>
<thead>
<tr>
<th>Sl.no</th>
<th>Plant name</th>
<th>Botanical name/ Family</th>
<th>Part used</th>
<th>Phytoconstituents</th>
<th>Therapeutic actions</th>
<th>Therapeutic uses</th>
</tr>
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<td>2.</td>
<td>Uttamani</td>
<td>Pergularia daemia/ Asclepiadeceae</td>
<td>Leaves</td>
<td>Sterols, Hentriacontane, Lupeol, B-amyrins, Calotropigenin, Calactin.</td>
<td>Expectorant, Emetic</td>
<td>Infantile diarrhea, Asthma</td>
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<td>7.</td>
<td>Mullangi</td>
<td>Raphanus sativus/Cruciferae</td>
<td>Leaves, Seeds, Root</td>
<td>Raphanin, Sulphoraphanin,</td>
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<td>10.</td>
<td>Udigai</td>
<td>Jasminum auriculatum /Oleaceae</td>
<td>Flowers, Roots</td>
<td>Indole, Methyl anthranilate.</td>
<td>Cordiotonic</td>
<td>Nephrolithiasis, Urolithiasis, Cardiopathy, Odontalgia</td>
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<td>11.</td>
<td>Ventayam</td>
<td>Trigonella foenum graecum / Papillionaceae</td>
<td>Seeds</td>
<td>Graecunin E, Trigocoumarin, Quercetin, P- Coumaric acid.</td>
<td>Anti diabetic, Diuretic, Anti spasmodic, Aphrodisiac.</td>
<td>Diabetes, Dysentery, Oxaluria, Nephrosis, Hypertension</td>
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<td>13.</td>
<td>Pushanikai</td>
<td>Benincasa hispida /Cucurbitaceae</td>
<td>Fruits, Seeds</td>
<td>Manitol, n- triacontanol, Lupeol, Protein, B-sitosterol</td>
<td>Diuretic, Anti pyretic</td>
<td>Haemoptysis, Other Haemorrhages from internal organs.</td>
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<td>No.</td>
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<td>Scientific Name</td>
<td>Part/Use</td>
<td>Active Constituents</td>
<td>Uses</td>
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<td>Nephrosis, Stone, Jaundice, Pancreatosis, Infertility.</td>
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<td>Shadavari</td>
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<td>Dysuria, Haematuria, Spermatorrhoea, Infertility-female, Tuberculosis.</td>
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<td>Bleeding piles, Wounds, Epilepsy, Hysteria, Haematuria.</td>
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<td>Anamia, Jaundice, Asthma, Ascites, Scanty urine.</td>
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<td>Cough, Nasal congestion, Throat infection.</td>
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<td>20.</td>
<td>Magilam</td>
<td>Mimusops elengi / Sapotaceae</td>
<td>Leaves, Bark, Seeds</td>
<td>Saponin</td>
<td>Astringent, Tonic</td>
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<td>Fever, Chronic dysentery.</td>
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<td>Painful and atonic dyspepsia, used in the dietary of sick.</td>
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<td></td>
<td>Plant Name</td>
<td>Scientific Name</td>
<td>Parts Used</td>
<td>Active Components/ Activity</td>
<td>Medical Uses</td>
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<td>27.</td>
<td>Maralingam</td>
<td>Crataeva nurvala</td>
<td>Fresh leaves, Roots, Stem bark</td>
<td>Varunol, Lupeol, Triterpenoids, Flavonoids- Rutin &amp; Quercetin</td>
<td>Diuretic, Litholitic, Natriuretic. Calculus, Bladder stone, Hydrocele, Nephrosis, UTI.</td>
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<td>28.</td>
<td>Sirupoolai</td>
<td>Aerva lanata</td>
<td>Whole plant</td>
<td>B-sitosterol</td>
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<td>Species</td>
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<td>Secondary Metabolites</td>
<td>Medicinal Action</td>
<td>Conditions</td>
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<td>29.</td>
<td><strong>Amarantaceae</strong></td>
<td></td>
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<td>palmitate, betlin, B-carboline, α-amyrin.</td>
<td>Nephroprotective.</td>
<td>Cough, Strangury, Lithiasis, Cough, Strangury, Lithiasis</td>
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</table>
CONCLUSION
This review indicates that all these herbs have possessed Diuretic, Lithotriptic, Nephro protective, Anti oxidant, Analgesic, Anti microbial, Anti spasmodic, effect and also used traditionally for many years in the treatment of Urolithiasis, Genito urinary tract diseases, Dysuria, Haematuria. Oliguria, and Kidney diseases. Therefore these herbs can be used for kidney stone disease as a single herbal drug or compound drug in the near feature.

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