Review Article

An Overview on Indian Medicinal Plants with Antiurolithiatic Activity

***Tushar Shelke, Sandesh Wayal, Shiv Gunjegaokar, Sachin Gaikwad, Amol Shirsath, Sunil Hadke**

Department of Pharmacology & Toxicology, JSPMs Charak College of Pharmacy and Research, Wagholi, Pune, Maharashtra 412 207, India.

ABSTRACT

Urolithiasis is one of the serious renal disorders that require a well targeted therapeutic strategy. A number of drugs including diuretics and stone inhibitors are available for the treatment of lithiaisis, but clinical evaluation of these drugs has shown incidence of relapses, side effects, and drug interactions. This has been the rationale for the development of new antilitiatic drugs and the search for novel molecules has been extended to herbal drugs that offer better protection and decreased relapse. Drugs of plant origin are gaining popularity and are being investigated for a number of disorders, including lithiasis. The present article reviews the antilithiatic activity of *Melia Azedarach* Linn., *Aerva lanata and Vediuppu chunnam in combination, Petroselinum sativum, Lagenaria siceraria, Hygrophila spinosa, Glochidion velutinium, Tinospora sinensis, Relith, Musa paradisica, Fenugreek, Tecoma stans, Celosia argentea, Plectranthus tomentora Hordeum vulgare* Linn., *Moringa oleifera* Lam., *Achyranthes aspera, Asparagus racemosus, Rubia cordifolia, Cucumis trigonus and Mimusops elengi.* The safest medicines than the allopathic medicines are Herbal system and here an attempt is made to review a some of phytoconstituents which is a potent antiurolithiatic and some medicinal herbs on which antiurolithiatic activity has been provedSome of the important plants reported for their antilithiatic activity have been highlighted in this study. Ayurvedic knowledge supported by modern science is necessary to isolate, characterise, and standardize the active constituents from herbal sources for antilithiatic activity.

Keywords: Medicinal plants, *Melia Azedarach* Linn., *Mimusops elengi* Urolithiaisis

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***Address for correspondence:**
Tushar Shelke,
Department of Pharmacology & Toxicology, JSPMs Charak College of Pharmacy and Research, Wagholi, Pune, Maharashtra 412 207, India.
E-mail: tushaarraj@rediffmail.com

INTRODUCTION

Kidney stones are small, hard deposits of mineral and acid salts developed from crystals that separate from the urine within the urinary tract. The most common type of stone contains calcium in combination with either oxalate or phosphate [1]. The problem of calculi formation is observed and reported in all parts of the urinary tract, the kidney, the ureter and the urinary bladder which may considerably vary in size [2]. The rate of occurrence is three times higher in men than women, because of enhancing capacity of testosterone and inhibiting capacity of oestrogen in stone formation [3]. Kidney stones are easy to diagnose for those with a sudden onset of pain, blood in the urine and stones that show on X-ray. Studies have shown that 15% of those with a stone develop another within a year and 33% within 5 years. These rates can be halved by drinking more than 2 liters of fluid each day. Some of the Indian medicinal plants and their derivatives have been an invaluable source of therapeutic agents to treat many disorders including urolithiasis. An indigenous drug possessing fewer side effects is the major thrust area of the present day research, aiming for a better and safer approach for management of lithiaisis [4]. This review summarises the features of some of the plants reported to possess antilithiatic activity. Although extensive research has been conducted in this area, recent studies with significant

findings involving of the plants are emphasized here.

MEDICINAL PLANTS POSSESING ANTILITHAITIC ACTIVITY

***Melia Azedarach* Linn.**

The effect of oral administration of aqueous and ethanol extracts of *Melia azedarach* Linn. leaves on calcium oxalate urolithiasis was investigated. Lithiasis was induced by oral adminstration of ethylene glycol (0.75 %v/v) in male albino rats for 28 days. Regular administration of ethylene glycol caused hyperoxaluria in ethylene glycol-fed animals, leading to increased renal retention and excretion of oxalate, calcium and phosphate. Oxalate and calcium excretion in urine increased in lithiatic control animals compared to for the normal control group. Treatment with aqueous or ethanol extract significantly reduced the elevated levels of calcium, oxalate and phosphate excretion in urine. The results demonstrated that the aqueous and ethanol extracts of *Melia azedarach* Linn leaves have potent antiurolithiatic activity against ethylene glycol-induced calcium oxalate urolithiasis in male albino rats [5].

Aerva lanata and Vediuppu chunnam

The efficacy of the two Siddha drugs, *Aerva lanata* and *Vediuppu chunnam* as antilithic agents using a urolithic rat model was tested. Hyperoxaluria was induced in rats using 0.75% ethylene glycol in drinking water. *Aerva lanata* and *Vediuppu chunnam* were given orally for 28 days. Urinary risk factors of urolithiasis were monitored at the end of 7th, 14th, 21st and 28th days. Urinary volume was increased in hyperoxaluric as well as drug-treated rats. Increased urinary excretion of calcium, oxalate, uric acid, phosphorus and protein in hyperoxaluric rats was brought down significantly by the administration of *A. lanata* or *Vediuppu chunnam*. Decreased magnesium excretion in hyperoxaluric rats was normalized by drug treatment. 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. Combination therapy was found to be more effective and this indigenous medicine can be used successfully as an antilithic agent [6].

Petroselinum Sativum

The presented study aimed to investigate the preventive effect of *Petroselinum sativum* on calcium oxalate calculi in rats. Forty-eight Wistar rats were divided into 6 groups: Group A served as normal control. Group B received 1% ethylene glycol in drinking water. Groups C, D, E, and F received 1% ethylene glycol from day 0 and were assigned as the prevention subjects. Rats in groups C and D received 200 and 600 mg/kg body weight of aerial parts aqueous extract respectively and those in groups E and F received 200 and 600 mg/kg body weight of root aqueous extract in drinking water respectively from the first day of the experiment. Serum levels of calcium decreased significantly, and that of the magnesium increased significantly. The number of calcium oxalate deposits significantly decreased in the prevention groups of C, D, E and F compared with group B on the 30th day. The weight of the kidneys decreased significantly in prevention groups [7].

Lagenaria siceraria

The study was intended to determine anti-urolithiatic effect of *Lagenaria siceraria* fruit powder (*LSFP*) against sodium oxalate (NaOx) induced urolithiasis in rats. Animals were grouped as Vehicle Group (received vehicle gum acacia 2% w/v 1 mL/kg/p.o.), NaOx Group (Sodium oxalate 70 mg/kg,i.p.), LSFP Group (500 mg/kg, p.o. LSFP suspended in gum acacia 2% + Sodium oxalate 70 mg/kg), Cystone Group (500 mg/kg, p.o. Cystone suspended in gum acacia 2% + Sodium oxalate 70 mg/kg). The increased severity of microscopic calcium oxalate crystals deposition along with increased concentration in the kidney was seen after 7 days of NaOx (70 mg/kg, i.p.) pre-treatment. *LSFP* (500 mg/kg, p.o.) and standard marketed formulation Cystone (500 mg/kg, p.o.) caused a significant reversal of NaOx-induced changes in ion excretion and urinary CaOx concentration in 7 days treatment. Finally it was concluded that *LSFP* showed beneficial effect against urolithiasis by decreasing CaOx excretion and preventing crystal deposition in the kidney tubules [8].

Hygrophila spinosa

The present study evaluated antiurolithiatic activity of methanolic extract of *Hygrophila spinosa*. Methanolic extract of the plant (250 and 500 mg/ kg body weight) was administered orally to male Wistar albino rats. Ethylene glycol (EG) was used to induce nephrolithiasis. The parameters studied included water intake, urinary volume, urinary pH, urinary and kidney oxalate and calcium, urinary magnesium and serum uric acid. Ethylene glycol feeding resulted in hyperoxaluria as well as increased renal excretion of calcium and serum uric acid along with decreased excretion of urinary magnesium. Treatment with HSME significantly reduced the elevated urinary oxalate, urinary calcium and serum uric acid with increase in reduced urinary magnesium. Ethylene glycol feeding also resulted in increased levels of calcium and oxalate in kidney which was decreased after the treatment with HSME. The increased deposition of stone forming constituents in the kidneys of ethylene glycol treated rats was significantly lowered by treatment with *Hygrophila spinosa* [9].

Glochidion velutinium

The aim of the study was to assess the effects of dried leaves of *Glochidion velutinium* (GV) as a preventive agent in experimentally induced urolithiasis model in rats. The efficacy of 250 and 500mg/kg GV extract was studied in 0.75% ethylene glycol and 1% ammonium chloride induced urolithiasis for 21 days in rats. The levels of calcium, phosphorus, oxalate in both 24h-urine & kidney were measured. The levels of BUN, creatinine and uric acid in serum were also measured. The increased levels of stone forming constituents in the kidneys of calculogenic rats was also significantly reduced by using methanolic extract of dried leaves of GV [10].

Tinospora sinensis

The presented study was an effort to evaluate the antiurolithiatic activity of *Tinospora sinensis* in ethylene glycol induced lithiasis in rats. Experimentally induced urolithiasis in rats was treated with standard drug cystone and trial drug *Tinospora sinensis* in two different doses (1ml and 2ml/kg). The calcium, phosphate and oxalate content in urine and kidney homogenate were determined and serum estimation of creatinine, uric acid and urea nitrogen were performed on 28 th day of experiment and were compared to the normal, control and standard drug group (cystone). The results suggested that *Tinospora sinensis* at the dose of 2ml/kg provided lowering effect of urinary stone forming constituents which was closer to standard group on dose dependent manner. So the present work was confirmed the traditional use of *Tinospora sinensis* for antiurolithiatic activity [11].

Relith

The antilithiatic effect of *Relith* a Polyherbal formulation was determined on ethylene glycol induced lithiasis in male albino rats. The lithiasis was induced to rats by oral consumption of ethylene glycolated water (0.75v/v) for 28 days. *Relith* (500mg/kg) was administered orally from 1st day for preventive regimen and from 15th day for curative regimen. The urinary ionic parameters were altered by ethylene glycol, which elevated the calcium, oxalate, inorganic phosphate, protein concentration in urine. The *Relith* significantly reduced the elevated levels of these ions and protein in urine. Also the extract significantly elevated the urinary concentration of magnesium. The elevated serum creatinine levels of lithiatic rats were reduced by prophylactic and curative regimen of extract treatment. The histological findings also showed improvement after treatment with the extract. These observations enable to conclude that the curative and preventive properties of *Relith* against ethylene glycol induced urolithiasis [12].

Musa paradisica

The effect of ethanol extract of dried roots of *Musa paradisica* Linn against ethylene glycol induced renal calculi in albino wistar rats were studied. A renal calculus was induced in rats by ingesting 0.75% ethylene glycol in drinking water for 28 days and was manifested by high urinary calcium, oxalate, and low urinary magnesium contents. Simultaneous administration of 1ml (1 in 10) *Musa paradisica* Linn orally for 28 days along with ethylene glycol (0.75% v/v) reduced urinary calcium, oxalate and elevated urinary magnesium level. It also

increased urinary volume thereby reducing the tendency for crystallization. The histopathological studies confirmed the induction as degenerated glomeruli, necrotic tubule and inflammatory cells was observed in section of kidney from animals treated with ethylene glycol. This was reduced; however after treatment with *Musa paradisica* Linn. These observations enable to conclude that *Musa paradisica* Linn is effective against ethylene glycol induced renal calculi [13].

Fenugreek

Therapeutic efficacy of standardized fenugreek seed extract with trigonelline as marker (SFSE-T) in experimental urolithiasis in rats was studied. Effects of subacute oral treatments of SFSE -T (30 and 60 mg/kg) and reference anti -urolithiasis drug, Cystone (750 mg/kg) were evaluated against 0.75% ethylene glycol (EG) and 1 % w/v ammonium chloride (AC) induced urolithiasis in rats. The biochemical (urinary and serum) and histopathological parameters were investigated. Subacute oral treatment of SFSE -T (60 mg/kg) showed reversal of EG+AC induced changes in urine (decreased 24-h urine output, pH, excretion of creatinine, citrate, and chloride and increased uric acid and oxalate excretion) and serum (increased creatine, uric acid and blood urea nitrogen) parameters and decreased creatine clearance. Histopathology examination of the kidneys sections from SFSE -T (60 mg/kg) treated rats showed lowered number of crystals, cell damage and tubulointerstitial damage index as compared with EG+AC control rats. Standardized fenugreek seed extracts showed promising therapeutic effect against experimental urolithiasis in rats [14].

Tecoma stans

Presented study evaluated the *Tecoma stans* flowers for their antiurolithiatic activity on experimentally induced urolithiatic rats. Antiurolithiatic activity of aqueous and methanolic extracts of *Tecoma stans* was carried out on ethylene glycol (0.75% v/v) induced urolithiasis in rats. Treatment with aqueous extract (200mg/kg, p.o) and methanolic extract (250mg/kg, p.o) of of *T.stans* flowers significantly lowered (P<0.001) the increased levels of oxalate, calcium and phosphate in urine and also significantly reduced (P<0.001) their retention in kidney. The treatment with aqueous extract and alcoholic extract of *Tecoma stans* flowers significantly (P<0.001) lowered the elevated serum levels of blood urea nitrogen, creatinine and uric acid in both regimens. The histopathological study of the kidney also supported the above results. The results were comparable to that of standard drug. The presented data indicate that administration of AETS and METS to rats with experimentally-induced urolithiasis reduced and also prevented the formation of urinary stones, supporting folk information regarding antiurolithiatic activity of the plant. The reduction in the stone forming constituents in urine and renal tissue brought about by *T.stans* could contribute to its antiurolithiatic property [15].

Celosia argentea

The study was mainly aimed to evaluate traditionally used *Celosia argentea* seeds for its antiurolithiatic activity.CA was used as diuretic therefore ethanolic extract of *Celosia argentea* seeds was scientifically evaluated to study antiurolithiatic activity at low dose (250 mg/kg; p.o.) and high dose (500 mg/kg; p.o.) in ethylene glycol (EG) induced urolithiasis in rats. At the end of the treatment changes in various physical parameters, promoters, inhibitors, renal function markers in urine and serum samples and antioxidant parameters and histopathology of kidneys were observed. Treated groups showed significant antiurolithiatic activity which was comparable with the standard drug [16].

Plectranthus tomentora

Present study was undertaken to evaluate the efficacy of *Plectranthus tomentora* in reducing the growth of calcium oxalate stones in ethylene glycol induced model. Upon administration of Furosemide (20mg/kg), aqueous extract of roots and seeds of *Plectranthus tomentora* (500 and 1000 mg/kg) on hyperoxaluria rats shows the significant activity in decrease kidney stones and serum levels (calcium, phosphorous, creatinine, urea) both not that as standard drug Furosemide [17].

***Hordeum vulgare* Linn.**

The ethanolic extract of seeds of *Hordeum vulgare* was tested in an animal model of urolithiasis induced by the addition of 3% glycolic acid to the normal diet of Wistar albino rats for a period of 42 days. The effects of EHV on various biochemical parameters were studied in urolithitic rats. There were significant elevated urine output, kidney weight loss and some renal injury markers in glycolic acid induced rats. In vivo antioxidant parameters including lipid peroxidation (MDA), superoxide dismutase (SOD) and catalase (CAT) were also determined. Oral administration of EHV 100, 250 and 500 inhibited CaOx crystal disposition in renal tubules and protected against associated changes in polyurea and kidney weight loss. EHV significantly maintained the urinary excretion of the calcium, phosphate, uric acid, urea, and oxalate and increased the excretion of citrate as compared to glycolic acid control animals. The increased deposition of stone forming constituents in the kidneys of calculogenic rats were significantly lowered by treatment with EHV. The extract also induced a significant decrease in MDA which increased in urolithiatic control rats. The extract also significantly increased SOD and CAT in urolithiatic rats which were markedly decreased in glycolic acid induced urolithiasis in rats [18].

***Moringa oleifera* Lam.**

The efficacy of the root bark of *Moringa oleifera* Lam. as an antiurolithiatic agent was investigated using an experimentally induced urolithiatic rat model. Hyperoxaluria was induced in rats using 0.75% ethylene glycol in water. Aqueous (AqE) and alcoholic extracts (AlcE) of the root bark of *M. oleifera* were given orally in curative and preventive regimens over a period of 28 days. Both the extracts significantly ($P<0.001$) lowered the urinary excretion and kidney retention levels of oxalate, calcium and phosphate. Moreover, elevated serum levels of urea nitrogen, creatinine and uric acid were significantly ($P<0.001$) reduced by the extracts. The results were comparable with the standard drug, cystone. 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 antiurolithiatic property of root bark of *M. oleifera* [19].

Achyranthes aspera

The present study was undertaken to evaluate the efficacy of *Achyranthes aspera* in preventing and reducing the growth of calcium oxalate stones in ethylene glycol induced nephrolithiatic model. Hyperoxaluria was induced in rats using ethylene glycol (EG, 0.4%) and ammonium chloride (1%) for 15 days and was then replaced with EG (0.4%) only. Upon administration of cystone (750 mg/kg body wt.), aqueous extract of A. aspera (500 and 1000 mg/kg body wt.), levels of renal injury markers (lactate dehydrogenase and alkaline phosphatase) were normalized with a decrease in serum urea and serum creatinine. Concurrent treatment reduced changes in the architecture of renal tissue and also decreased the size of crystals thereby helping in quick expulsion of the crystals. The present results indicated that *Achyranthes aspera* had an ability to maintain renal functioning and reduced renal injury [20].

Asparagus racemosus

The study was undertaken to evaluate the efficacy of *Asparagus racemosus* against experimentally induced urolithiaisis. Thirty-six male Wistar albino rats were randomly divided into six groups. Ethylene glycol (EG) 0.75% and ammonium chloride (AC) 2% in drinking water were fed to all groups (Groups II–VI) except normal control (Group I) rats for 10 days to induce urolithiasis. Group III–VI rats were treated with ethanolic extract of *Asparagus racemosus* (EAR)at doses 200, 400, 800, and 1600 mg/kg, respectively, for 10 days. Positive control (Group II) rats were treated with EG/AC alone. Group I rats were administered drinking water and distilled water (6 µl/g) by gavage. After 10 days, blood samples were collected and analyzed for serum concentrations of calcium, phosphorus, urea, and creatinine. The kidneys were removed and sectioned for histopathological examination. The increased deposition of stone forming

constituents in the kidneys of calculogenic rats were significantly lowered by treatment with EAR [21].

Rubia cordifolia

The study investigated the protective effect of the hydro-alcoholic extract of roots of *Rubia cordifolia* Linn. (HARC) against ethylene glycol induced urolithiasis and its possible underlying mechanisms using male Wistar albino rats. Ethylene glycol feeding resulted in hyperoxaluria, hypocalciuria as well as increased renal excretion of phosphate. Supplementation with HARC significantly prevented change in urinary calcium, oxalate and phosphate excretion dose-dependently. The increased calcium and oxalate levels and number of calcium oxalate crystals deposits in the kidney tissue of calculogenic rats were significantly reverted by HARC treatment. The HARC supplementation also prevents the impairment of renal functions. Indicate that the HARC can protect against ethylene glycol induced urolithiasis as it reduced and prevented the growth of urinary stones [22].

Cucumis trigonus

Effect of ethanolic fruit extract of *Cucumis trigonus* Roxb. on antioxidants and lipid peroxidation in urolithiasis induced wistar albino rats was studued. Urolithiasis was induced using ethylene glycol in wistar albino rats, the formation of calcium stones in the kidney results with the damage of antioxidant system. Ethanolic extract of *Cucumis trigonus* Roxb fruit of family Curcurbitaceae was used to treat urolithiasis. On this course, the extract also repairs the changes that happened in the enzymatic, non enzymatic antioxidants and lipid peroxidation in liver and kidney of urolithiasis induced rats [23].

Mimusops elengi

Petroleum ether, chloroform, and alcohol extracts of *Mimusops elengi* bark were evaluated for antiurolithiatic and antioxidant activity in male albino Wistar rats. Ethylene glycol (0.75%) in drinking water was fed to all the groups (Groups II-IX) except normal control (Group I) for 28 days to induce urolithiasis for curative (CR) and preventive (PR) regimen. Groups IV, V, and VI served as CR, and groups VII, VIII, and IX as PR were treated with different extracts of M. elengi bark. Groups I, II, and III served as normal control, positive control (hyperurolithiatic), and standard (cystone 750 mg/kg), respectively. Oxalate, calcium, and phosphate were monitored in the urine and kidney. Serum BUN, creatinine, and uric acid were also recorded. In vivo antioxidant parameters such as lipid peroxidation (MDA), glutathione (GSH), superoxide dismutase (SOD), and catalase (CAT) were also monitored. All the extracts of *M. elengi* were safe orally and exhibited no gross behavioral changes in the rats. In hypercalculi animals, the oxalate, calcium, and phosphate excretion grossly increased. However, the increased deposition of stone forming constituents in the kidneys of calculogenic rats was significantly lowered [24].

CONCLUSION

According to the old hypothesis, calculi aggregation was thought to be the sole cause of lithiasis formation and reduction in saturation of the substances producing or enhancing calculi was thought to be the major approach towards therapy. However, in the light of recent evidences this concept has changed. Now, treatment of renal stone mainly targets the potentiation of the defensive system along with lowering of lith formation. Chemical substances derived from plants have been used to treat human diseases since the dawn of medicine. Roughly 50% of new chemical entities introduced during the past two decades are from natural products. Recent technological advances have renewed interest in natural products in drug discovery. Therefore, efforts should be directed towards isolation and characterization of the active principles and elucidation of the relationship between structure and activity. Furthermore, detailed analysis of the active constituents of natural drugs should be directed towards clinical relevance. Standardization is indispensable to maintain reproducible quality in biological evaluation. Ayurveda, the oldest medicinal system in the world, provides leads to find therapeutically useful compounds from plants. Therefore, ayurvedic knowledge supported by modern science is necessary to isolate, characterise, and standardize the active constituents

from herbal source. This combination of traditional and modern knowledge can produce better antiulcer drugs with fewer side effects. Herbs are widely available in India and other countries. The wide spectrum makes them attractive candidates for further research.

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