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Antiurolithiatic activity of natural remedies with emphasis on their mechanisms of action: A review

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Abstract

Urinary calculi are the third most prevalent disorder of the urinary tract and nearly 80% of these calculi are composed of calcium oxalate. There are very few drugs available for the management of urolithiasis. Medicinal plants contained many constituents that work with minimum side effects and are available to a large population. The current review focused on antiurolithiatic of natural sources, hoping that it was beneficial for general public and it attract the researchers for antiurolithiatic drug discovery.

Keywords: Antiurolithiatic; Natural; Medicinal Plants; Mechanisms

1. Introduction

Urinary stones were found in the tombs of Egyptian mummies dating back to 4000 BC and in the graves of North American Indians from 1500 to 1000 BC. Stone formation was mentioned in the early Sanskrit documents in India between 3000 and 2000 BC [1]. Urinary tract stone is an oldest disease known to man. It occurred in 12% of the global population and its re-occurrence rate in males is 70-81% and 47-60% in female [2-3]. Calcium-containing stones, are the most commonly occurring urinary stons (75-90%) followed by magnesium ammonium phosphate (10-15%), uric acid (3-10%) and cystine 0.5-1% [4-5]. Drug prescribed for the treatment of renal stone dependent on the type of the stone and the patient characteristics. Thiazide diuretics are commonly used to reduce the risk of calcium stone recurrence [6-7]. Xanthine oxidase inhibitors are used in patients with hyperuricosuria and either uric acid or calcium stones [8-9]. Urinary alkalinizers are used in patients with hypocitriuria [10-11]. Cystinuria treatment involves hydration to reduce cystine concentration and reduced oral intake of sodium and protein. Urinary alkalinization is the next step, aiming to increase the solubility of cystine. Potassium citrate, is frequently utilized [12-13].

The previous pharmacological studies revealed that many medicinal plants can induce antiurolithiatic effects by many mechanisms. Some of medicinal plants possessed antiurolithiatic effect by their diuretic action, the increase in urine volume decreases the saturation of the salts and prevents the precipitation of the crystals at physiological pH. Increase of the quantity of fluid going pass through the kidneys enhanced the flush out the deposits. Some of plant altered the ionic composition of urine (decreasing the calcium and oxalate ion concentration, increasing magnesium and citrate excretion) [14-16].

Others exert their antiurolithiatic effect via inhibition of nucleation, growth, and aggregation of the crystals. Furthermore, some of plants induced alkalinization of the urine and increased solubility of the deposits[17].

The development of botanical medicine as an alternative or supplement to the conventional medicine system has attracted great interest and served as a considerable source of new drugs. The current review was designed to discuss the natural remedies with antiurolithiatic activity.

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2. Medicinal plants with antiurolithiatic effects

2.1.1. Adiantum capillus-veneris

The hydro alcoholic extract of *A. capillus-veneris* Linn. on calcium oxalate crystallisation was evaluated by *in vitro* study. Crystallization was induced by addition of 50 µl of 0.1 M sodium oxalate in whole urine in the absence and the presence of extract at different concentrations (0.50 mg, 0.75 mg and 1 mg). The nucleation and aggregation rates were followed at 620 nm after mixing calcium chloride and sodium oxalate solution and in a buffered solution containing calcium oxalate monohydrate crystals, respectively. The rate was evaluated by comparing the slope of turbidity in the presence of extract with that of control using the spectrophotometer. Crystals in the urine were also analysed by light microscopy. Extract of the test drug inhibited the crystallization in solution; less and smaller particles were observed in the presence of extract. These results were further confirmed in the nucleation assay, though the rate of nucleation was not inhibited but number of crystals was found to be decreased. The extracts also inhibited crystal aggregation[18]. The result of significant in vitro inhibitory effects on crystallization and aggregation was further confirmed by *in vivo* study against ethylene glycol (0.75%) and ammonium chloride (1%) induced urolithiasis in male Sprague Dawley rats. Urine microscopy showed significant reduction ($p<0.001$) in the number of crystals. Serum levels of calcium, phosphorous, and blood urea were found to be decreased significantly. Serum creatinine level was found to be similar to plain control. The animals treated with test drug showed much improvement in body weight. Histopathology of kidney showed almost normal kidney architecture in treated groups [19-22].

2.1.2. Adonis aestivalis

In lithiasis induced by feeding the rats with 0.75% ethylene glycolated water for 28 days. Ethylene glycol treatment raised the urinary calcium, phosphate, oxalate and protein levels significantly ($p< 0.05$) in the lithiatic group, where magnesium level showed a significant decrease. However, after the treatment with *Adonis aestivalis* (divided doses of extract of 60 mg/kg of body weight daily by gavages). *Adonis aestivalis* attenuated the elevated parameters and inhibit stone formation [23-24].

2.1.3. Agrimonia eupatoria

Significant uricolytic activity has been documented for agrimony infusions and decoctions (15% w/v), following their oral administration to male rats at a dose of 20 ml/kg body weight (equivalent to 3 g dry plant powder)[25-26].

2.1.4. Althaea rosea

In both preventive and curative protocols, treatment of rats with hydroalcoholic extract of *Althaea rosea* roots significantly reduced the kidney calcium oxalate deposits compared to ethylene glycol group. Administration of *Althaea rosea* extract also reduced the elevated urinary oxalate due to ethylene glycol [27-28].

2.1.5. Ammannia baccifera

Prasad *et al* tested the antiurolithic activity of *A. baccifera* in male albino rats. Urinary stones were induced by implantation of zinc discs in the urinary bladder. They found that the ethanolic extract of *A. baccifera* (2g/kg/day, po) was effective in reducing the formation of stone and also in dissolving the pre-formed one. There was a significant increase in the urinary excretion of calcium, magnesium and oxalate, four weeks after implantation of zinc discs. Treatment with *A. baccifera* has significantly reduced calcium and magnesium levels in the prophylactic group while it has reversed the levels of these ions to normal values in the curative group [29-30].

2.1.6. Ammi visnaga

Ammi visnaga was investigated for the preventive effect of kidney stone formation. In cell culture experiments, it was found that *Ammi visnaga* and its compounds (khellin and visnagin) protected cell damage from calcium oxalyate crystals. In addition, *Ammi visnaga* and its compounds prevented calcium oxalyate crystals formation in stone forming rats by increasing the urinary pH and citrate concentration along with a decrease of urinary oxalate. The calcium oxalyate crystals deposition in the rat kidneys was significantly decreased in the group of rats receiving *Ammi visnaga* and its compounds [31].

The oral administration of an aqueous extract prepared from the fruits of A. visnaga as well as two major constituents khellin and visnagin prevent crystal deposition in stone-forming rats. Hyperoxaluria was induced in male Sprague-Dawley rats by giving 0.75% ethylene glycol and 1% ammonium chloride via the drinking water. The Khella extract (KE; 125, 250 or 500 mg/kg) was orally administered for 14 days. The histopathological examination of the kidneys revealed

that KE significantly reduced the incidence of calcium oxalate (CaOx) crystal deposition. In addition, KE significantly increased urinary excretion of citrate along with a decrease of oxalate excretion. Comparable to the extract, khellin and visnagin significantly reduced the incidence of CaOx deposition in the kidneys. However, both compounds did not affect urinary citrate or oxalate excretion indicating a mechanism of action that differs from that of the extract. For KE, a reasonably good correlation was observed between the incidence of crystal deposition, the increase in citrate excretion and urine pH suggesting a mechanisms that may interfere with citrate reabsorption [32]. The prophylactic effects of *Ammi visnaga* may be attributed to its diuretic activity to maintain the oxalate, below the supersaturation to precipitate as Calcium oxalate [33-34].

2.1.7. Benincasa hispida

Benincasa hispida fruit rind extract (outer thick pericarp) was also significantly increased ($p<0.001$) urine volume, sodium and chloride levels, and significant decrease ($p<0.001$) potassium excretion in rats when used orally in a dose of 100 mg/kg bw [35]. When 0.75% v/v ethylene glycol was given to the rats in drinking water to induce chronic hyperoxaluria, with simultaneous *Benincasa hispida* extract at the dose of 250 and 500 mg/kg bw, orally for 35 days. The supplementation with *Benincasa hispida* extract significantly lowered the urinary excretion and kidney retention levels of oxalate, protein and calcium. Moreover, elevated serum levels of sodium, creatinine, calcium and phosphorus were significantly reduced by the extracts [36-37].

2.1.8. Carthmus tinctorius

The effects of Floscarthami (FC) (600 and 1200 mg/day, by gastric gavages), was evaluated on calcium oxalate (CaOx) formation in ethylene glycol (EG)-fed rats. 24-h urine and blood samples were analyzed at the beginning and end of the experiment. Kidney tissue was histopathologically examined using a polarized light microscope, and crystal deposits were evaluated by a semi-quantitative scoring method; these scores were significantly lower in the FC groups (600 and 1200 mg/day) than in the placebo group[38-39].

2.1.9. Desmostachya bipinnata

Desmostachya bipinnata alone and in combination with *Brassica oleracea* possessed antiurolithiatic effect on experimentally-induced urolithiasis in rats by ethylene glycol (0.75% v/v) with ammonium chloride (1% w/v) in drinking water for ten days . The aqueous extracts of both plants were administered separately and in combination to urolithiatic rats at a dose of 400 mg/kg for 10 days. Daily oral treatments with extracts were insignificantly decreased the quantity of calcium oxalate deposited in the kidneys, but they reverted all the biochemical changes compared with control [40-41].

2.1.10. Dolichos lablab

Antilithiatic study revealed that the methanolic extract of white and black seeds of *Dolichos lablab* possessed antilithiatic activity, but less than that recorded for the extract of leaves and bulbs of *Nymphaea odorata* [42-43].

2.1.11. Helianthus annuus

The effect of aqueous and ethanolic extracts (500 mg each for 10 days) of *Helianthus annuus* leaves on calcium oxalate nephrolithiasis was studied in male rats. Ethylene glycol and ammonium chloride feeding resulted in hyperoxaluria as well as increased renal excretion of calcium and phosphorus. The increased deposition of stone forming constituents in the kidneys of calculogenic rats was significantly lowered by treatment with aqueous and ethanolic extracts [44-45].

2.1.12. Herniaria hirsuta

Herniaria hirsuta was evaluated in nephrolithiasis in rats as a preventive agent against the development of kidney stones. The experiment was conducted in normal and calcium oxalate (CaOx) nephrolithiasic rats during 3 weeks. The results showed that water intake and urinary volume increased in nephrolithiasic rats, but their urinary pH decreased especially in the third week of treatment. Urinary oxalate increased significantly during the second week in untreated rats and remained constant in rats treated with Herniaria decoction. However, urinary calcium decreased significantly in week 2 in untreated rats and remained constant in the treated rats. Qualitative analysis of crystalluria showed that untreated rats excreted large CaOx monohydrate and few dihydrate crystals while treated animals excreted small CaOx dihydrate crystals mostly. The examination of kidney sections revealed that CaOx deposition was decreased in the treated compared to untreated rats [46].

The effect of a botanical formulation of *Herniaria glabra*, *Agropyron repens*, *Equisetum arvense,* and *Sambucus nigra* was studied as a preventive agent in an experimentally induced urolithiasis model in rats (0.75% ethylene glycol (EG) and

1% ammonium chloride for three days). Rats were treated with 30 mg/Kg, 60 mg/Kg, 125 mg/Kg, 250 mg/Kg and 500 mg/Kg of the plant extract formulation (PEF). Animals treated with 125 mg/Kg of the PEF had statistically significantly lower calcium oxalate crystals deposits content compared to the control group. All PEF doses statistically significantly decreased the number of microcalcifications compared to the control group. Furthermore, the number of kidneys showed subcapsular fibrosis was significantly higher in control group than in treated groups with the PEF. The diuresis of the 125 mg/Kg and 500 mg/Kg PEF-treated groups was statistically significantly higher than that of the control group [47].

The effects of *Herniaria hirsuta* L. (Carryophyllaceae) and Agropyron repens L. (Gramineae), as herb infusion, combined with different diets (standard, high glucidic, high protein) on the calcium oxalate urolithiasis were studied in rats. The results revealed that the antilithiasic effects of the H. hirsuta infusion clearly depends on the diet. Thus, a clear increase in the citraturia was only detected when such infusion was administered with the high protein diet [48].

The effectiveness of an extract of *Herniaria hirsuta* on calcium oxalate crystallization was studied in vitro. Crystallization was induced in whole normal human urine samples in the absence or presence of the extract. Crystals generated in the urine were harvested and analysed by scanning electron microscopy. The nucleation and aggregation of calcium oxalate crystals were measured separately using spectrophotometric methods. The herb extract promoted the precipitation of calcium oxalate particles in whole urine. The results showed the extract of *H. hirsuta* promoted the nucleation of calcium oxalate crystals, increasing their number but decreasing their size. It also promoted the formation of calcium oxalate dihydrate crystals, despite the presence of calcium oxalate monohydrate particles. The extract may contain substances that inhibit calcium oxalate crystal aggregation [49].

The prophylactic effect of oral administration of *Herniaria hirsute* decoction was investigated in experimentally induced calcium oxalate (CaOx) nephrolithiasis in rats. *H. hirsuta* has an impressive prophylactic effect on CaOx stones in nephrolithic rats, the effect which did not mediated by biochemical or diuretic changes [50].

Cystine stones represent 1% of urinary calculi in adults and 10% in children and are especially recurrent and resistant. In Morocco, various plants, *Herniaria hirsuta*, Opuntia ficus-indica, Zea mays and Ammi visnaga were used against nephrolithiasis. The effect of plant extracts on the disolution of cystine stones was studied in vitro. The results revealed that the studied herbal extracts were efficient for dissolving cystine stones, probably by formation of complexes between cystine and polyhydroxylated molecules present in the extracts [51].

The interaction of calcium oxalate crystals with renal epithelial cells is a critical event in kidney stone formation. The effect of aqueous extract from *Herniaria hirsuta* on the adhesion of calcium oxalate monohydrate (COM) crystals to cultured renal cells was investigated. Calcium oxalate monohydrate crystal binding to cells was inhibited by extract in a concentration dependent manner. It was suggested that the extract may coats the crystals and inhibits their attachment to cells [52].

The methanol extract of *Herniaria hirsuta* was fractionated determine the nature of compound responsible for the beneficial effect of *Herniaria hirsuta* in prevention and cure of urolithiasis. The fractions were then assayed on calcium oxalate crystallization in *in vitro* and *in vivo* models. In the whole human urine, only the fraction eluted with ethanol/water was associated to formation of smaller crystals composed of calcium oxalate dihydrate, similarly to the aqueous extract. When tested at 5 mg/day, it reduced significantly crystal deposition in lithiasic rats. Preliminary identification of the fraction showed the presence of saponins which may be responsible for the beneficial effect of Herniaria hirsuta in the treatment of kidney stones [53-54].

2.1.13. Hibiscus rosa-sinensis

The aqueous extract of flowers of *Hibiscus rosa-sinensis* was evaluated for antilithatic potential in vitro. The presence of calcium oxalate crystals was evaluated immediately and after 24 hrs of stone induction. Crystal aggregation after 24 hrs was inhibited by Hibiscus rosa-sinensis extract. The extract interfered with early stages of stone formation and may represent an alternative form of treatment and or prevention for urolithiasis [55-56].

2.1.14. Hibiscus sabdariffa

Supplementation of aqueous extract of *Hibiscus sabdariffa* at different doses (250, 500 and 750 mg/kg body weight) significantly lowered the deposition of stone-forming constituents in the kidneys and serum of urolithiatic rats. These findings were confirmed by the histological investigations [57-58].

2.1.15. Juniperus communis

The antiurolithiasis and dissolution of urinary stones of *Juniperus communis* fruit extract was studied in vitro. Variable concentrations of some fractions of the extract of Juniperus communis fruit (500, 1000 and 2000 µg/ml solutions) were used in vitro on urinary stones brought out from human kidney. Neutral (normal saline), positive (sodium bicarbonate) and negative (acetic acid) control groups were also tested. Significant findings were obtained in urinary stones composed of calcium oxalate (50%), calcium hydrogen phosphate (20%), magnesium ammonium phosphate, (10%) and ammonium urate (20%). The weight of dry powder of stones in normal saline decreased from 1458 mg to 1162, 1124, 1136, 1144, 1096, 1126, and 1130 mg after exposure to increasing concentrations of some fractions of the extract of Juniperus fruit. In addition, the ratio of calcium oxalate in normal saline aqueous solution plus stone increased from 70% to 80% after using some fractions of the extract of Juniperus fruit [59-60].

2.1.16. Lantana camara

The antiurolithiatic activity of ethanolic extract of roots (200mg/kg) and oleanolic acid (60-100mg/kg) isolated from roots of *Lantana camara* was studied in albino male rats using zinc disc implantation induced urolithiatic model. The group in which only zinc disc was implanted without any treatment showed increase in calcium output (23 ± 2.7mg/dl). Cystone receiving animals showed significant protection ($p < 0.01$). Treatment with oleanolic acid and ethanolic extract of roots significantly reduced the calcium output at dose of oleanolic acid 60 mg/kg ($p < 0.01$), oleanolic acid 80mg/kg ($p< 0.01$), ethanolic extract of roots 200mg/kg ($p< 0.01$), and oleanolic acid 100mg/kg ($p< 0.001$), as compared with zinc disc implanted group. The rats received oleanolic acid and ethanolic extract of roots also showed reduced formation of depositions around the zinc disc ($p< 0.001$) [43].

Ethanolic extract of *Lantana camara* leaves were evaluated for antiurolithiatic activity against 0.75% v/v ethylene glycol and 2% w/v ammonium chloride induced calcium oxalate urolithiasis and antioxidant activity against hyperoxaluria induced oxidative stress in male albino rats. Extract caused significant reduction in the deposition of calcium, oxalate and also urinary excretion of calcium, oxalate and creatinine, indicating its antiurolithiatic effect. It also decreased the extent of lipid peroxidation and enhanced the levels of antioxidant enzymes in the kidneys of urolithic rats, reflecting its antioxidant efficacy against hyperoxaluria induced renal oxidative stress [61-62].

2.1.17. Lawsonia inermis

The curative and protective effects of the alcoholic extract of *Lawsonia inermis* bark against ethylene glycol induced urolithiasis and its possible underlying mechanisms were studied in rats. Methanolic extract of *Lawsonia inermis* (MELI) bark (300 and500 mg/kg, po) were administered once daily from 15^{th} day to 28^{th} day as curative regimen and from 1^{st} day to 28^{th} day as preventive regimen. Treatment with the extract significantly restored all elevated parameters including calcium, phosphate and oxalate in urine and kidney homogenate; and creatinine, uric acid and urea nitrogen in serum compared to control group. The histopathological study of the kidney also supported the biochemical results [63].

The antiurolithiatic activity of hydroethanolic extract of the leaves of *Lawsonia inermis* was studied in ethylene glycol with ammonium chloride model in rats. Hydroethanolic extract showed significant antiurolithiatic activity against calcium oxalate type stone. It modulated the levels of serum urea, urea nitrogen, uric acid, creatinine, kidney weight, urine volume, urine PH, urinary total protein, calcium, phosphorus and magnesium [64-65].

2.1.18. Lippia nodiflora

Lippia nodiflora ethanol extract exhibited antiurolithiatic effect. The extract significantly prevented the formation of the calcium oxonate stone, dissolved the pre-formed calcium oxolate stone in the kidney of rats induced by gentamycin and calculi producing diet due to its ability to increase the urinary pH and excretion of the calcium and oxolate, and also to reduce the urine super-saturation with the calculogenic ions [66-67].

2.1.19. Malva neglecta

The anti-urolithiasis effects of aqueous extracts of *Malva neglecta* (intraperitoneal injections of 200 and 800 mg/kg for 28 days) was investigated in ethylene glycol and ammonium chloride induced kidney stones in rats. The extract significantly decreased CaOx deposits and tubule-interstitial damage ($p<0.001$) in the preventive groups. In curative groups, a low dosage of extract, reduced kidney oxalate deposits and tubule-interstitial damage ($p<0.05$). However, high dosed was more effective in both preventive and curative groups ($p \leq 0.001$) [68-69].

2.1.20. Melia azedarach

The antilithiatic effect of the aqueous extract of *Melia azedarach* was studied against ethylene glycol- induced nephrolithiasis in male albino rats. Simultaneous administration of aqueous extract of *Melia azedarach* (250 mg/kg bw, orally for 28 days) with ethylene glycol (0.75%) reduced urinary calcium, oxalate, phosphate, and elevated urinary magnesium level. It also increased the urine volume, thereby reducing the tendency for crystallization. Histopathologically, the microcrystal deposition was reduced after treatment with the extract [70].

2.1.21. Musa paradisiaca

The efficacy of antiurolithiatic effect of the aqueous-ethanol extract of *Musa paradisiaca* was studied in urolithiasis induced in hyperoxaluric rat model using ethylene glycol for 28 days along with 1% ammonium chloride for the first 14 days. Administration of ethylene glycol and ammonium chloride resulted in increased crystalluria and oxaluria, hypercalciuria, polyuria, crystal deposition in urine, raised serum urea, and creatinine as well as nitric oxide concentration and erythrocytic lipid peroxidation. The aqueous-ethanol extract of *Musa paradisiaca* significantly restored the impairment in kidney function test as that of standard treatment, cystone in a dose-dependent manner [71].

2.1.22. Nasturtium officinale

The protective effects of hydrophilic extract of *Nasturtium officinale* (750 mg/kg and 1.5 g/kg of extract) on ethylene glycol-induced renal stone was studied in rats. Percentage of calcium oxalate crystals in negative control groups was 75%, in preventive groups treated with low dose (28.6%) and high dose (57.1%) in comparison to healthy control group (12.5%). Urinary oxalate concentration in preventive and negative control groups were more than healthy control group ($P< 0.05$) [72-73].

2.1.23. Oreganum vulgare

The antiurolithic effect of the crude aqueous- methanolic extract of *Oreganum vulgare* was studied using *in vitro* and *in vivo* methods. In the *in vitro* experiments, kidney epithelial cell lines (MDCK) and urinary bladder of rabbits were used, whereas, in the *in vivo* studies, rat model of urolithiasis was carried out to study the preventive and curative effect of the extract. In the *in vitro* experiments, the extract exhibited a concentration-dependent (0.25-4 mg/ml) inhibitory effect on the slope of nucleation and aggregation and also decreased the number of calcium oxalate monohydrate crystals (COM) produced in calcium oxalate metastable solutions. It also showed concentration-dependent antioxidant effect. The extract reduced the cell toxicity and LDH release in renal epithelial cells (MDCK) exposed to oxalate crystals. The extract also relaxed high K^+ induced contraction in rabbit urinary bladder strips. In male Wistar rats receiving lithogenic treatment, the extract treatment (10-30 mg/kg) prevented as well as reversed toxic changes including loss of body weight, polyurea, crystalluria, oxaluria, raised serum urea and creatinine levels and crystal deposition in kidneys compared to their respective controls [74].

2.1.24. Oxalis corniculata

Struvite stones were grown in a gel medium by *in vitro* single diffusion gel growth technique. The aqueous extract of *Oxalis corniculata* effectively repressed the growth of struvite stones and led to the dissolution of stones, the inhibitory effect was further enhanced by its biofabricated AgNPs [75].

2.1.25. Plantago major

The *in vitro* effect of *Plantago major* extract on calcium oxalate crystals was investigated. The concentrations of*Plantago major* extract used were from 100ppm to 350ppm. Extract of *Plantago major* has inhibitory effect on the number of crystals but it was not significant. However, extract of*Plantago major* was better than allopurinol and potassium citrate in inhibiting the size of the calcium oxalate crystal *in-vitro*[76].

2.1.26. Polygonum aviculare

The protective effects of *Polygonum aviculare* aqueous extract (100 and 400 mg/kg, orally as preventive and therapeutic remedies) on urolithiasis induced by ethylene glycol and ammonium chloride were studied in rats. The number of CaOx crystals and tubulointerstitial changes were significantly increased in the induction groups, and significantly declined in the prevention and therapeutic groups [77-78].

2.1.27. Portulaca oleracea

The antiurolithiasis activity of the ethanolic extract of aerial parts of *Portulaca oleracea* Linn was studied using the ethylene glycol (0.75% v/v) and ammonium chloride (2% w/v) induced urolithiasis model in albino rats. Several parameters were used including urinary volume, urine pH, urine and serum parameters to assess the activity. The ethanolic extract of *Portulaca oleracea* was administered in doses of 100, 200 and 400 mg/kg body weight orally for 15 days. Standard drug used was cystone. Treatment with the extract restored all the elevated biochemical parameters including serum and urine (calcium, creatinine, urea, BUN), restored the urine pH to normal and increased the urine volume significantly ($P < 0.05$) when compared to disease control group. The histopathological studies confirmed the induction of lithiasis as microcrystal deposition was observed in section of kidney from animals treated with ethylene glycol and ammonium chloride. This was reduced, after treatment with the extract [79].

2.1.28. Prunus mahaleb

The effect of *Prunus mahaleb* seed methanolic extract on ethylene glycol- and ammonium chloride-induced urolithiasis was studied in BALB/c mice. The extract was effective in prevention the formation of kidney stones. Mice treated with *Prunus mahaleb* extract in a dose of 500 mg/kg dose showed less damage to the kidney with remarkable decrease of the serum parameters. The acute toxicity test showed that the use of the extract was safe in mice [80].

2.1.29. Punica granatum

Animals model of calcium oxalate urolithiasis was was used to evaluate the anti-urolithiatic effect of Punica granatum. Chloroform extract (PGCE) and methanol extract (PGME) were given orally at 100, 200 and 400mg/kg, along with ethylene glycol for 28 days. On 28 day, 24h urine was collected from individual rats and used for estimation of urine calcium, phosphate and oxalate. The serum creatinine, urea and uric acid levels were estimated for each animal. The kidney homogenate was used for the estimation of renal oxalate contents. The paraffin kidney sections were prepared to observe the CaOx deposits. The ethylene glycol control caused significant ($P<0.001$ vs. normal) increase in levels of urine oxalate, calcium and phosphate, serum creatinine, urea and uric acid and renal tissues oxalates, as compared to normal. The paraffin kidney sections show significant histopathological changes. The treatment of PGCE and PGME at 100, 200 and 400mg/kg doses, significantly ($P<0.001$ vs. control) decreased the urine oxalate, calcium and phosphate, renal tissue oxalates and serum creatinine, urea and uric acid after 28 days [81].

2.1.30. Quercus Spp

Ninty seven patients suffering from urolithiasis were treated with Litiax. 82 of them presented ureteral stones and the other 15 kidney stones. The product was administered in doses of 1350 mg/ day. The treatment lasted between 8 and 225 days, the average duration being 58 days. It was revealed from the results obtained that the product tested has an inhibiting effect on the growth of the stone, antiinflammatory and diuretic. It also seems to inhibit the bacteria proliferation to a certain extent. The product is easily tolerated [82].

2.1.31. Terminalia chebula

The antiurolithiatic property of aqueous extract of fruit of *Terminaliachebula* in Wistar albino rats. The protective effect of aqueous extract of *Terminaliachebula* fruit was evaluated at two dose levels (100 and 200mg/kg body weight) using ethylene glycol induced calcium oxalate urolithiasis model in rats. The results indicate that ethylene glycol treatment decreases calcium level in urine and increased it in the kidney tissue homogenate, which were prevented in animal receiving simultaneous treatment of extract. Extract treatment 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 creatinine, uric acid and blood urea nitrogen. Histopathological study revealed that extract reduced histological changes and retained the normal architecture of kidney tissue [83].

2.1.32. Trigonella foenum-graecum

The therapeutic efficacy of standardized fenugreek seed extract with trigonelline as marker (SFSE-T) was evaluated in experimental urolithiasis in rats. 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 [84].

3. Conclusion

The pharmacological researches claim that many plants are useful for the treatment of urinary tract stones. The main difficulties in developing a standard anti-uriolithic drug may be the multi-etiological nature of urolithiasis, the various biochemical disorders that lead to urolithiasis, and the different chemical types of kidney stones. The present review has highlighted the medicinal plants that have been evaluated against many types of kidney stones, by various experimental models of urolithiasis.

Compliance with ethical standards

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