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# CURRENT STATUS OF UROLITHIASIS AND ITS TREATMENT WITH PHYTOMEDICINE

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Phytoleads, Urolithiasis, Phytomedicine, Prevalence

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**ABSTRACT:** Urolithiasis is the one of the old diseases in humans. Renal stones are a common problem worldwide, affecting all geographical regions with substantial morbidities and economic costs. The main aim of this article to review the recent research on urolithiasis to treat with medicinal plants that are present in India. In this article, review the recent prevalence data of urolithiasis in India. The study explores the efficacy and availability of the herbal treatment of urolithiasis. Plants are available in nature; safest mode of treatment and Cost-effectiveness may enable improvements in treatment efficiency that can benefit Patients and the healthcare system. This study elaborates the recent research in treating urolithiasis with medicinal plants and their phytoleads. Compile research work's *in-vitro* and *in-vivo* data and highlight their methods and results. The average life time risk of stone formation has been reported in the 5-10% range. Recurrent stone formation is a common part of the medical care of patients with stone diseases. Herbal medicine has several phytoleads and exert their pharmacological action in urolithiasis by multiple mechanism like, help in passage of stone by increasing urine volume, pH, and diuretic activity and balance the inhibitor and promoter of the crystallization in urine and affecting the crystal nucleation, aggregation and growth. This review focuses on the several plants with their urolithiasis activity treated with multiple mechanisms and analyses the incidence of urolithiasis in India, according to recent research.

**INTRODUCTION:** Stone formation in the kidney is one of man's oldest and most widespread diseases. The deposition or formation of stones in any part of the urinary system *i.e.* the kidney, the ureters or the urinary bladder is called urolithiasis. A stone is an aggregation of solute materials from urine such as calcium, oxalate, phosphate and uric acid which forms stone. In India, calcium oxalate is found to be the most predominant constituent of urolithiasis.

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Stone formation is the culmination of a series of physiochemical events, *i.e.*, supersaturation and nucleation, crystal growth, and aggregation that occurs as the glomerular filtrate traverses through the tubules of nephron [1]. Urolithiasis is a worldwide problem with significant health and economic burdens. Medical therapy that alters the course of stone disease has enormous medical and financial impact.

Current regimens are based mostly on rational alteration of urinary biochemistry and physical chemistry to lower the risk of precipitation. Kidney stones are quite common and usually affect people who are between 30 and 60 years of age [2]. They affect men more than women. It is estimated that renal colic (severe pain caused by a kidney stone) affects about 10-20% of men and 3-5% of women.

In most countries with a relatively high incidence of renal calculi due to climate, diet habits, local geology with hydro mineralogy and sanitation by affecting geominerology. Rising global temperatures could lead to an increase in kidney stones. Dehydration has been linked to stone disease, particularly in warmer climates, and global warming will exacerbate this effect. The correlation between increased environmental temperature and increased number of stone events supports the conclusion that global warming impacts the development of stones [2].

Calcium oxalate stones represent up to 80% of analysed stones. Calcium phosphate account for 15-25%, while 10-15% is mixed stones. The others are struvite 15-30%, cystine 6-10%, and uric acid stones 2-10% (4). Calcium oxalate stones are of primary two types, calcium oxalate monohydrate (whewellite) and calcium oxalate dihydrate (weddellite). The occurrence frequency of whewellite is 78% while that of weddellite is 43% [3].

In India, in the Ayurvedic system of medicine, 'Pashanabheda' group plants, claimed to be useful in the treatment of urinary stones. 'Pashanabheda' is the Sanskrit term used for a group of plants with diuretic and antiurolithiatic activities. It has been estimated that 80% of the world's population relies on traditional medicine to treat their `diseases. Medicinal plants have a long history of use and are globally safer than synthetic drugs. They are a reliable source for drug discovery. Today, researchers have focused on the drug discovery from medicinal plants. It has been estimated that at least one third of all medicinal product have plant origin. Medicinal plants are regarded as an acceptable, cheap, easily available and safe source of active compounds for pharmaceuticals. The therapeutic effects of medicinal plants on kidney and urinary tract disorders have been variously studied and their efficacy has been demonstrated [4].

Prevalence of urolithiasis in India-In the most part of India, urolithiasis is prevalent, with an expectancy of 12% in a total population reported to be prone to urinary stones. In 12% of affected population, 50% of the population are severely affected by renal damage, which even leads to a loss of kidneys [5]. Unlike in South India, where kidney stone cases are reported low percentages. According to the research articles in south India, among 666 urolithiatic patients, 430 were males (64.56%) and 236 were females (35.44%). The male female ratio was 1.82:1. It has been found that renal calculi is more prevalent between the age of 20 and 40. In given data all the renal calculi patients were literate and most of the patients (55.70%) belonged to upper socioeconomic family.

Out of 666 patients, found (43.24%) patients had already stones in their life time. (23.12%) patients had family history of kidney stone. (72.07%) patients did not drink required water (2-3 lit/day) daily. (67.56%) patients sweat a lot every day. (24.77%) patients were used NSAID frequently for pain. We also found that (36.03%) patients have the habits of smoking and (41.59%) patients have the habits of alcohol consumption. (42.79%) patients were lacking physical activity. (34.08%) patients were associated with hypertension, (26.72%) patients were associated with Diabetes and (15.91%) patients were associated with UTI.

In northern India, there is a 15% of the population is affected by urolithiasis in north cities of India, out of 621 patients, 313 (50.4%) were males and the male-to-female ratio was 1.01:1. The mean age of the patients was 42.88 ± 14.78 years and most of the patients (25.12%) were between age group 31 and 40 years. Housewife as occupation was the most common (37.2%) patient. Most of the patients (57.8%) were asymptomatic with flank pain present in 35.6% patients. 42.8% of patients had a family history of urolithiasis. 63.1% of the population had single stone, commonly seen in 31–40 years of age, whereas multiple stones were found mostly in 41–50 years of age group. The Kidney was the most common site of calculus, affecting in (67.4%) of cases.

Upper 1/3 ureter (16.6%), middle 1/3 ureter (2.1%), lower 1/3 ureter (5.5%), and vesical(2.6%) followed in frequency. Stones present at two or more sites were in (5.5%) of patients. The incidence of urolithiasis differs according to location. A study reported 75.08% renal stones, 13.62% were ureteric stones, 9.56% had stones at vesico-ureteric junction (VUJ), and 1.74% had bladder stones [6]. Stone formation in the urinary tract has been recognized for thousands of years,

but during the last few decades the pattern and incidence of the disease have changed markedly. Urinary stone affect 10-12% of the population in industrialized countries. The average lifetime risk of stone formation has been reported in the 5-10% range. Recurrent stone formation is a common part of the medical care of patients with all types of stone disease. The incidence of Urinary stones has been increasing recently. With a prevalence of >10% and an expected recurrence rate of nearly 50%, stone disease has an important effect on the health care system. Thus, considering the prospects of the kidney stone belt, which is affected by urolithiasis in India, a proper corollary needs to be established. The most affected states of India with urolithiasis are Maharashtra, Gujarat, Rajasthan, Punjab, Haryana, Delhi, Madhya Pradesh, Bihar, and West Bengal [7-8.]

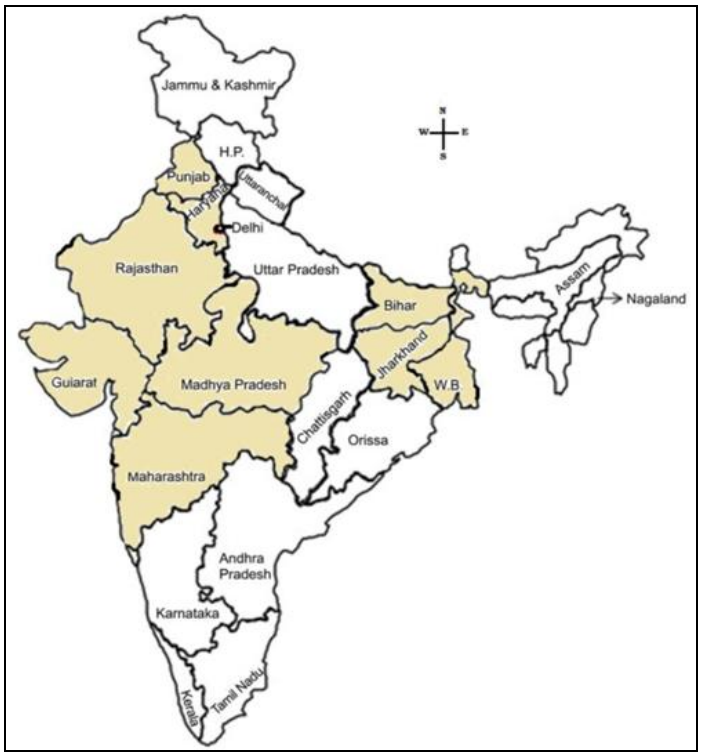


**FIG. 1: MAJOR KIDNEY STONE PREVALENT STATES IN THE INDIA**

Urolithiasis is prevalent all over the world in Asia, the prevalence and incidence of urolithiasis have increased in most of the countries of Asia over the last several decades [9]. The highest prevalence rate was seen in West, South and Southeast Asia. Calcium oxalate, which is still the dominant component of stones, is rising in proportion to the whole calculi. The prevalence of urolithiasis has increased significantly in the last few decades in most Asian countries, like China (from 4% to 6.4%), Japan (from 4.3% to 9.0%), South Korea (from 3.5% to 11.5%), Thailand (from 1.4% to 16.9%), Saudi Arabia (from 6.8% to 19.1%), Iran (from 5.7% to 8.1%) and Israel (from 1.2% to 9.2%) [10]. In north America found that, kidney stones occurred in 5.2% of adults between the ages of 20 and 74 year from 1988 to 1994 [11]. In 2007 to 2010, the prevalence increased to 8.8% in this period. Patients in the southern USA suffered higher rates of urolithiasis than those in the west or northeast [12].

**Role of Phytomedicine in Urolithiasis:** Herbal medicine is an integral part of the development of modern civilization. Various medicinal plants are used in urolithiasis, and their effect is documented [9]. According to the World Health Organization, plants provide an economical and affordable source of drugs for three-quarters of the world population [10] and their therapeutic use is increasing. The research work on some medicinal plants and their phytoleads with promising their result of their work are listed in below.

***Aerva lanata*:** two isolated compounds (quercetin and betulin) of *A. lanata* were screened for antiurolithiatic potentials in calculi-induced (ethylene glycol 0.75% v/v) male wistar albino rats

by administering 2 mg/kg b.w/day orally as test dose for 28 days. Significant reduction in the size of calculi and significantly enhanced excretion of calcium, oxalate, phosphate. SEM of kidney sections has revealed reduction in the calculi in treated animals [11].

***Dolichos biflorus*:** *Dolichos biflorus* seed has antinephrolithiatic and antioxidative efficacy. Ethylene glycol caused a significant increase in calcium, oxalate, phosphate, and total protein in urine and the kidney, whereas a decrease in calcium, sodium, and magnesium in serum was observed. Ethylene glycol also caused a significant increase in lipid peroxidation and a concurrent decrease in the activities of antioxidant enzymes in the kidney. However, the seed extract of *D. biflorus* caused significant restoration of all these parameters (p50.001). Histopathological and histochemical studies also showed reduced calcifications in the kidney of seed extract-treated rats [12].

***Asparagus racemosus*:** Parts used are leaves. Common name is Nunggarei-angouba. Its chemical constituents are tannic acid, volatile oil, mucilage, saponin, flavonoids, asparagine, sitosterol, sapogenin, and asparagenin. It is useful in expelling stones from the urinary tract. Its pharmacological activities are antispasmodic, aphrodisiac, demulcent, antibacterial, diuretic, anti-diarrheal, antitumor, expectorant, antiepileptic, galactagogue, stomachic, anti-inflammatory, appetizer, and tonic. *A. racemosus* was investigated for its inhibitory effect on stone formation.

Lithiasis was induced by administering 0.75 % ethylene glycolated water to adult male albino rats orally for 28 days. Ethylene glycol altered the urine chemistry by elevating the phosphate, oxalate, and calcium levels responsible for kidney stones. Phosphate, calcium, and oxalate levels were decreased by using ethanolic extract of *Asparagus racemosus.* This extract and magnesium level also reduced creatinine level was increased which is an inhibitor of stone formation. The histological finding shows that *Asparagus racemosus* improves signs of deterioration induced by ethylene glycol. These observations show that *Asparagus racemosus* inhibits ethylene glycol-induced stone formation [13].

***Terminalia arjuna*:** Parts used are leaves. The common name is Arjun. Its chemical constituents are arjunetin, friedelin, beta-sitosterol, arjunic acid and ellagic acid. It is used in hyperlipidemia and cardiovascular disorders. Its pharmacological activities are hypo-cholesterolemic and cardioprotective. Bark of *Terminalia arjuna* was investigated for its inhibitory effect on calcium oxalate and calcium phosphate crystal formation. Fraction of solvent and crude extract of this plant was used for inhibitory activity. This study was done in vitro. This study indicated that bark of Terminalia arjuna has potential to inhibit calcium oxalate and calcium phosphate crystal formation. Most effective fraction of *Terminalia arjuna* was butanol [14].

***Bryophyllum pinnatum:*** *B. pinnatum* (Crassulaceae), is commonly known as ‘life plant’ or ‘air plant’ is native to India, China, Australia, New Zealand, and Philippines. *B. pinnatum* was found to reduce crystal size and promote the formation of calcium oxalate dihydrate crystals instead of monohydrate crystals under *in-vitro* studies.

The calcium oxalate dihydrate crystals are considered as less urolithic since they do not damage the epithelial lining of urinary tract [15]. In another study, administration of aqueous extract of leaves of *B. pinnatum* (50 and 100 mg/kg b.w., i.p.) found to significantly reduce the urinary oxalate and kidney calcium absorption levels, which were elevated due to simultaneous administration of 1% (v/v) ethylene glycol in rats [16].

***Bergenia ligulata:*** *B. ligulata* (Saxifragaceae) is a well-documented Ayurveda plant commonly known as Paashaanbhed. The traditional antilithiatic claim of rhizomes of *B. ligulata* has been validated under both *in-vitro* and *in-vivo* animal studies showed that detannated deproteinized extract of *B. ligulata* (5ml of 0.1g/ml solution) had significant calcium and phosphate precipitation inhibitory potential than whole plant extract, under *in-vitro* [17]. Another study reported that calcium oxalate crystal aggregation inhibitory potential to aqueous-methanolic extract of *B. ligulata* rhizome (BLR). In same study, BLR (5–10 mg/kg) found to prevent calcium oxalate crystal deposition in the rat renal tubules.

Authors concluded that *B. ligulata* may mediated antiurolithic activity through its calcium oxalate crystal inhibition, diuretic, hypermagneseuric and antioxidant effects [18].

***Tribulus terresteris:*** *T. terrestris* (Zygophyllaceae) is locally named as Gokhru or Gokshur in India. It is a highly prescribed plant in the Ayurvedic system of medicine for the cure of urinary stones. Current *in-vitro* studies demonstrated that the aqueous extract of *T. terrestris* fruit inhibited the nucleation and growth of the calcium oxalate crystals. In addition, it found to have a cytoprotective role in NRK 52E cells, which was mediated by lowering LDH leakage and increasing the cell viability [19].

The antiurolithic potential of the fruits of *T. terrestris* has also been confirmed an albino rat model. An antilithiatic protein of molecular weight of ~ 60kDa has been purified from *T. terrestris* [20]. Besides these potent antilithiatic effects, some nephrotoxic concerns have been recently come forwarded about *T. terrestris* [21].

***Ammannia baccifera L:*** *A. baccifera* L. (Lythraceae) is a widely distributed plant species in the tropical regions of Asia, America and Africa. It is an accredited plant in Ayurveda and TCM for the treatment of various ailments including urolithiasis. The oral administration of ethanolic extract of *A. baccifera* (2 g/kg/day) was effective in reducing the formation of stones and dissolving the pre-formed ones in albino rats [22].

***Stevia rebaudiana:*** Ethanolic extract of *stevia rebaudianabertoni (Asteraceae)* leaves against ethylene glycol-induced nephrolithiasis in albino rats. Ethanolic extract (100 mg/kg b.w.) Of *S. Rebaudiana* leaves significantly reduced the elevated urinary oxalate. calculogenic rats was significantly lowered by curative and preventive treatment using ethanolic extract of *S. rebaudiana* leaves [23].

***Trigonella foenum:*** In this research evaluate effect of fenugreek on ethylene glycol induce kidney stone in rats. Regarding the other drugs, such as Cystone, the seeds of *Trigonella foenumgraecum* (fenugreek) are reported to have been used as anti-urolithiatic in traditional medicine. Thus, the present study was undertaken to investigate the effect of fenugreek on the prevention of kidney stone formation. Twenty male albino rats were divided into 4 groups: Normal, Ethylene Glycol (EG), Cystone and Fenugreek. The duration of the experiment was 28 days. Ethylene glycol group led to increases in kidney weight, malondialdehyde (MDA) and platelet count, while Cystone and Fenugreek combat the effect of EG. Haematological examination showed that the haemoglobin and red blood cell count in rats treated EG were significantly lower than those in the controls while Fenugreek and Cystone decreased the EG effect.

Our studies demonstrate the anti-urolithiatic and antioxidative potential effects of T. *foenum-graecum*, which could exert beneficial effects against the kidney stone formation and the associated free radicals' complications in kidney tissues. Further clinical trials are needed for evaluating its benefits and the possible side effects [24].

***Solanum xanthocarpum:*** Nephrolithiasis was induced in male Wistar rats by adding ethylene glycol (0.75%) in drinking water for 28 days. Animals were divided into six groups, each containing six *viz*. Vehicle control, model control, *S. xanthocarpum* methanol extract in different doses of 100, 200, and 400 mg/kg p.o., Cystone (750 mg/kg, p.o.) served as a standard. Hyperoxaluria as well as an increase in the excretion of calcium, phosphate, uric acid and decrease in citrate and magnesium in urine, impairment of renal function and oxidative imbalance in kidney were observed in the calculi-induced group. Treatment with *S. xanthocarpum* decreases hyperoxaluria, +calcium, and uric acid, improves renal function, and also produces antioxidant effects. Crystalluria was characterized by excretion calcium oxalate (CaOX) crystals, which were enormous in the lithogenic group but smaller in the drug-treated group. The histology showed that the calculi-induced group had a large deposition of CaOX crystals in kidney while the treated group had trivial and fewer deposits.

The result indicates the antiurolithiatic activity of *S. xanthocarpum* mediated possibly by CaOX crystal inhibition, diuretic, antioxidant and maintaining balance between stone promoter and inhibitor

constituents, and this study rationalized its medicinal use in urolithiasis [25].

***Moringa oleifera:*** In this study evaluate the Antiurolithiatic activity of aqueous extract of bark of *moringa oleifera (lam.*) in rats. aqueous extract of bark of *Moringa oleifera* administered orally, was evaluated for its antiurolithiatic potential in albino rats of Wistar strains. The stones were produced in this study by zinc disc foreign body insertion in the bladder supplemented with 1% ethylene glycol in drinking water. The reduction in weight of the stones was used as criteria for assessing the preventive or curative antiurolithiatic effect of the bark of this plant. Two doses of extract for prophylactic and curative groups were used. In both groups the oral ad-mination of the extract of bark of *Moringa oleifera* has resulted in significant reduction in the weight of bladder stones compared to the control group [26].

***Duranta erecta:*** This study was performed to investigate the anti-urolithiatic activity of methanolic extract of *Duranta erecta* leaves by in vitro and in vivo analysis. The study was designed to determine presence of phytochemicals in *D. erecta*, its yield in percentage, antioxidant activity against 2, 2-diphenyl-1-picrylhydrazyl (DPPH) and anti-microbial property against few bacteria. In vitro analysis was carried out study anti-urolithiatic property of *D. erecta* by nucleation assay and synthetic urine assay for inhibition of calcium oxalate and calcium oxalate monohydrate crystals formation. An *in-vivo* experiment was performed on Wistar rats for confirmation of anti-urolithiatic property of *D. erecta* in animal model. *D. Erecta* has the presence of primary and secondary metabolites like glycoside, saponins, sterols, flavonoids, phenols, tannins, alkaloids, carbohydrates and proteins. Methanolic extract of *D. erecta* gave a very good yield (60%). *D. erecta* proved its antioxidant potential by 93.51% inhibition of DPPH radical at a concentration of 1000 mg/mL where ascorbic showed 94.71% of DPPH radical at the same concentration. *In-vitro* tests like nucleation and synthetic urine assays showed that *D. erecta* inhibits formation of calcium oxalate and calcium oxalate monohydrate crystals. It also showed the anti-microbial property by formation of zone of inhibition against few bacteria. An *in-vivo* experiment on Wistar rat animal model confirmed the anti-urolithiatic property of *D. erecta* L. leaves extract [27].

***Solanum nigrum:*** In this study they investigate the Anti-urolithiatic activity of *Solanum nigrum* hydroalcoholic extract in ethylene glycol-induced urolithiasis in rats. Urolithiasis was induced by oral administration of ammonium chloride 1% and ethylene glycol (0.75% v/v) in drinking water for 28 days. Hydroalcoholic extract of *Solanum nigrum* fruit (200 and 400 mg/kg) and cystone (750 mg/kg) were administered orally from the 15th day as a curative regimen. Administration of ethylene glycol caused an elevation of serum creatinine, urea, calcium, and malondialdehyde and a reduction of magnesium and glutathione. In addition, renal content of tumor necrosis factor alpha was elevated and adiponectin renal content was reduced in urolithiatic control. Histopathological examination revealed tubular degeneration, dilatation, presence of calcium oxalate crystals in the lumen of renal tubules, and intense interstitial mononuclear cell infiltration in the lithiatic control group. Treatment with both doses of *Solanum nigrum* reversed all biochemical parameters and histopathological alterations. The results demonstrate that the hydroalcoholic extract of *Solanum nigrum* has potent anti-urolithiatic activity against calcium oxalate urolithiasis induced by ethylene glycol through tumor necrosis factor alpha inhibition and adiponectin stimulation as well as in maintaining balance between stone promoter (calcium) and inhibitor (magnesium) [28].

***Biophytum senstivum:*** In recent research, the *Biophytum senstivum* has antiurolithic and antioxidant activity of ethanol extract of whole plantin ethylene-glycol (EG)-induced urolithiasis in Wistar albino rats. EG 0.75% v/v in drinking water was fed to all groups, except the control group for 28 days to induce urolithiasis in rats. Groups I, II, and III served as control, toxic control, and standard Cystone groups, respectively. Animals in Group IV were administered with EEBS from 15th day to 28th day, while Group V animals were administered with EEBS from 1st day to 28th day. Several renal functional and injury markers in urine and serum were determined. Antioxidant enzyme activities were also recorded. Co-administration with EEBS (ethanolic extract of *Biophytum senstivum*) exhibited protective effect against

EG-induced proteinuria, hypercalciuria, hypomagnesuria hypercalcemia, and hyperphosphatemia. Serum protein levels were significantly increased, whereas blood urea nitrogen, creatinine, and uric acid levels were significantly lowered. EEBS-treated rats significantly attenuated the aberrations in the antioxidant enzyme activities, body weight, kidney weight, urine output, and urine pH compared to toxic control animals. Hence, this study confirmed the usefulness of *B. sensitivum* as an antiurolithic and antioxidant agent [29].

***Chenopodium album:*** In resent study of *Chenopodium album*, investigated the effect of methanolic and aqueous extracts of leaves of *Chenopodium album* on experimentally-induced urolithiasis in rats to substantiate its traditional use as antilithiatic agent. The leaf extract was standardized by HPLC. Urolithiasis was induced in rats by administration of 0.75% v/v of ethylene glycol (EG) in distilled water and in addition, vehicle or methanol (CAME) or aqueous (CAAE) extract of the leaves of *Chenopodium album* each in the dose 100, 200 and 400 mg/kg or Cystone (750 mg/kg) were administered daily orally for 28 days. Urolithiasis was assessed by estimating the calcium, phosphorus, urea, uric acid, and creatinine in both urine and plasma.

The volume, pH and oxalate levels were also estimated in urine. The renal oxalate content was estimated in kidney while calcium oxalate deposits were observed histologically. The treatment with CAME or CAAE for 28 days significantly attenuated the EG-induced elevations in the urine and plasma levels of calcium, phosphorus, urea, uric acid and creatinine along with decrease in urine volume, pH and oxalates. The treatments also decreased renal tissue oxalate and deposition of oxalate crystals in kidney due to EG treatment. The effects of CAME and CAAE were comparable to standard antilithiatic agent, cystone. The findings indicate the preventive effect of CAME and CAAE which can be due to inhibitory effect on crystallization and stone dissolution. The effect was attributed to the presence of phytochemicals like flavonoids and saponins. Chenopodium album leaves exhibited antilithiatic effect and validates its ethnomedicinal use in urinary disorders and kidney stones [30].

***Thinopyrum intermedium:*** The recent study on thinopyrum intermedium is, to evaluate *in-vitro* urolithiasis activity of *Thinopyrum intermedium* on experimentally prepared calcium oxalate crystals. Calcium oxalate crystals were prepared by homogenous ppt method by using calcium chloride and sodium oxalate. the crude extract was prepared by the simple maceration with methanol 1:3 ratio and the solvent were evaporated by rotary evaporator and two doses of extract selected i. e. 10mg and 20mg and compared against standard cytosine all were assayed against calcium oxalate crystals which were incubated in semipermeable membrane with sulphuric acid. The results were 68.02% (10mg), 72.41% (20mg) and 90% and we conclude that the *Thinopyrum intermedium* was showed significant effect of urolithiasis [31].

***Mangifera indica:*** *Mangifera indica* seeds (MIS) are used traditionally for treating multiple ailments including urolithiasis. In current study, aqueous methanolic extract of MIS was examined for antiurolithiatic potential against Calcium oxalate (CaOx) crystals. *In-vitro* analysis (nucleation, aggregation and growth assays) was performed with 20, 40, 60, 80 and 100 mg/mL concentrations of extract against standard drug (cystone).

*In-vivo* CaOx crystals were induced by administration of drinking water comprising 0.75% v/v ethylene glycol (EG) and 1% w/v ammonium chloride (AC) for initial 3 days followed by intake of 0.75% v/v EG for next 25 days. Total 36 rats were allocated into 6 groups receiving vehicle, EG + AC, Cystone and extract (250, 500 and 1000 mg/kg) respectively. Urine and blood samples were collected for biochemical analysis. In *in-vitro* analysis, 1000 mg/mL concentration significantly inhibited crystal formation when compared to standard. While MISE (500 and 1000 mg/kg) produced significant reduction in serum creatinine, BUN and uric acid levels while increased urine volume, Mg, pH and citrate levels of urine in MISE treated rats. The results give a scientific basis for its traditional claims [32].

***Berberis asiatica*:** In this research of *berberis asiatica* is to explore the antiurolithiatic ability of bioactive compounds of *Berberis asiatica* loaded Chitosan nanoparticles (BACBANPs) toward ethylene glycol engendered renal calculi in albino

Wister rat species. Calcium oxalate renal calculi were activated by ingestion of 0.75% (v/v) ethylene glycol and 1% (w/v) ammonium chloride in male Wister rats. Reference standard Cystone; bioactive compounds of *B. asiatica* (BACBA) and BACBANPs were provided at oral dose of 750 mg/kg, 400 mg/kg and 400 mg equivalent weight of BACBANPs/kg, respectively.

The curative and prophylactic consequences of BACBANPs were estimated. Urinary variables include calcium, magnesium, uric acid, phosphate and oxalate; intensification of oxalate and calcium in the kidney; and serum uric acid, creatinine, calcium, and blood urea nitrogen were evaluated. Creatinine clearance has been computed. Specifications of *In-vivo* antioxidant investigations include reduced glutathione, superoxide dismutase, lipid peroxidation, and catalase; and histopathological studies of the kidney were analyzed. After treated with cystone, BACBA, and BACBANPs, the serum, urine parameters, and *in-vivo* antioxidant specifications were almost normalized in prophylactic and curative regimens compared to control groups. Loading of BACBA in Chitosan nanoparticles in which Chitosan serves as a ligand to megalin receptors on renal epithelial cells contributes to targeting and promotes the accumulation of BACBA than administered alone. It was concluded that the antiurolithiatic activity of BACBANPs was substantially escalated in comparison to BACBA and cystone [33].

***Apium graveolens:*** The anti-urolithiasis activity of *Apium graveolens* seeds is may be due to the presence of flavonoids and tannins. Animals were divided in to 5 groups. Group I-Control, Group II-Negative control, Group III-Treated with standard drug, Group IV-Treated with Lower dose. Group-IV Treated with higher dose. Data comparison was made between Group I – Group V Urolithiasis was induced by feeding Ethylene glycol with ammonium chloride for 28 days. Statistical significance was done by ANOVA, followed by Dunnett's multiple comparison test CaOx and CaP deposition in the kidneys of EG and ammonium chloride fed animals. Treatment with EEAG (200/400 mg/kg) for 14 days successfully prevented the elevation of deposition of CaOx, phosphate in kidney when compared to the standard drug. Significant decrease in Body weight, Feed intake, water intake observed in EG fed animals. Treatment with EEAG (200/400 mg/kg) for 14 days successfully increases the Body weight, water intake and food intake, when compared to the standard drug. Increased urinary excretion of urinary calcium, oxalate, and phosphate are observed in EG and ammonium chloride fed animals.

Treatment with EEAG (200/400 mg/kg) for 14 days successfully decreased the excretion of oxalate, calcium, phosphate when compared to the standard drug. Serum creatinine, uric acid, Urea increased in EG and ammonium chloride fed animals due to decreased GFR. Treatment with EEAG (200/400 mg/kg) for 14 days successfully decreases the serum creatinine, uric acid, Urea when compared to standard drug. Histopathological findings of the EG fed animals are distended tubules, dilation and deposition of crystals. The histopathology of kidney was brought to normal in EEAG treated animals when compared to the standard drug. The present study indicates that the administration of EEAG to rats in ethylene glycol and ammonium chloride induced urolithiasis reduces the growth and development of kidney stones by reducing the stone forming constituents by increasing the GFR. Accordingly, it can be concluded that the supplementation of Apium graveolens has a beneficial effect on urolithiasis. Further studies are needed to identify the molecular mechanism of Apium graveolens and the structural elucidation of phytoconstituents responsible for antiurolithiasis [34].

***Annona squamosa:*** In resent study**,** evaluate the antiurolithiatic activity of Annona on ethylene glycol induced urolithiaisis in rabbits. Twenty-five rabbits were divided into five groups: (GI, control group) 5 rabbits untreated with Ethylene glycol and (GII) 5 rabbits were give 0.75 % Ethylene glycol in drinking water only for 30 days, while (GIII, GIV and GV) 15 rabbits were giving 0.75 % Ethylene glycol in drinking water and oral supplementation of Annona (flavonoids, glycosides and alkaloids) extracts(100mg /kg Bw) two times daily for 30 days. Blood samples were collected (plain tube & EDTA tube) to clinical examination. EG induced significant reduction (20%) in rabbits BW in G II in comparison with GI, GIII, GIV and GV. The result show, AST, ALT, ALKP, TBIL, MDA,

SOD, urea, creatinine, globulin and monocytesin G II were significantly elevated (P=0.05); meanwhile there were significant decrease (P=0.05) in total protein, albumin, A/G ratio, Gpx, CAT, GSH, BP, Hb, WBC and RBC. But after treatment by extracts of Annona significant reduction in AST, ALKP, TBIL, MDA, urea, creatinine and monocytes, while SOD, ALT no significant decrease. Meanwhile there were significant increase (P=0.05) in total protein, A/G ratio, Gpx, GSH, BP, Hb, WBC and RBC [35].

***Bombax ceiba:*** Parts used are seeds. It contains tannin, quercetin, kaempferol, shamimin, mangiferin, naphthalene derivatives, phenolic compounds, proteins, lupeol, phytosterols, beta sitosterol, glycosides, and alkaloids. It is used in dysuria, strangury, chronic inflammation, and calculous affections. Its pharmacological activities are antioxidant, hypoglycemic, analgesic, anti-inflammatory, hypotensive, cardiac stimulant, cytotoxic, diuretic, and antioxidant [40].

**DISCUSSION AND CONCLUSION:** Epidemiological studies of nephrolithiasis have demonstrated increasing prevalence and incidence of the disease over the last several decades. Although men continue to be affected more often, women are increasingly closing the gender gap. urolithiasis is associated with chronic kidney dysfunction, bone loss and fractures, increased risk of coronary artery disease, hypertension, type 2 diabetes mellitus and the metabolic syndrome. Nephrolithiasis places a significant burden on the health care system, which is likely to increase with time. Kidney stone formation is a multifactorial disease that can be influenced both positively and negatively by diet. Renal calculi are crystalline structures associated risk factors *i.e.*, dehydration, high fat diet, animal protein, high salt intake and obesity. Diet and fluid intake are important factors out of several other factors that can promote or inhibit kidney stone formation. When take diet with high volume of salts and high protein intake, and lack of fluid intake, chance to cause renal stone. According to recent data of prevalence of urolithiasis, 12% of the population of India are affected by urolithiasis. 50% of affected people are causing to renal damage and probable leads to kidney failure and associated with other diseases like, coronary artery disease, and type 2 diabetes mellitus. Antiurolithiatic activity has been documented to several plants and their formulations in the several ancient texts. However, only few plants and herbal formulations have been studied in order to accredit their traditionally known antiurolithiatic claim so far. These include, *Aervala nata, Dolichos biflorus, asparagus racemosustermenalia arjuna, Bryophyllum pinnatum, Terbulus terresteis, Ammania bacifera, Bergenia ligulata, stevia rebaudiana, trigonellafoenum, Solanum xanthocarpum, Moringa oliefera, Duranta erecta, Solanum nigrum, Biophytum senstivum, Chenopodium album, Thinipyrum intermedium, Mangifera indica, Berberis asistica, Apium graveolens, Annona, bombax ceiba.* The majority of these antiurolithiatic plants found to either dissolve the stones in urinary system and expel out or inhibit the process of urinary stone formation, so the development of calculi has been stopped. However, these plants safe and effectiveness against urolithiasis, these plants or their phytoleads are antiuolithiatic agents.

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