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A BRIEF REVIEW ON MECHANISM AND ROLE OF HERBAL EXTRACTS IN THE TREATMENT OF CALCIUM OXALATE KIDNEY STONES THROUGH IN-VIVO ANIMAL STUDIES

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ABSTRACT

Calcium oxalate stones are the major kidney stones as they are the product of the residue of the urinary contents which got precipitated, crystallized, aggregated and reserved in the kidney. The occurrence of these stones depends on certain factors genetics and age. The major term used for kidney stones is 'Urolithiasis' and the main allopathic treatment which is available in the market is Allopurinol, Zonisamide. The allopathic drugs are having certain limitation so herbal plants are good sources to overcome this problem. There are so many herbal treatments available for kidney stones like extracts of tulsi, *Foeniculum vulgare, etc.* Some of them are also tested in the preclinical trials because they do not cause any allergy and tiredness. The present review gives an idea on the various herbal extract that is tested on the animal model and they elimate the growth of the calcium oxalate stones by the various mechanism. This article gives information about the animal model, model for inducing the stones like ethylene glycol, ammonium chloride, etc in the animal model along with the uses of the model.

KEYWORDS: Calcium oxalate, kidney stones, animal model, plant extracts.

1. INTRODUCTION

Kidney stones are called renal stones which are formed when crystals get aggregated in the kidneys. Kidney stones normally excreted from the body by the process of urination and many stones are delivered and surrendered without causing side effects. In the event that stones develop to bounty measure before entry, on the request of no less than 2-3 millimeters, they can cause hindrance of the ureter. Additionally, a kidney stone is characterized as a hard mass created from stones that different from the urine inside the urinary tract Regularly, urine contains chemicals that keep or restrain the stones from the urinary tract.[1,2] Kidney calculi frame in the kidneys because of precipitation of urinary constituents and may create in either of the kidneys.[3] when the mineral present in urine is in large amounts then it leads to the formation of stones. The determination is normally in light of manifestations, testing of urine, and medical/restorative imaging. Blood tests may likewise be useful.[4] Urolithiasis, otherwise called the development of urinary stones, is a medical issue that influences all populaces around the world, saving no topographical, social, or racial gatherings. The yearly frequency of nephrolithiasis is evaluated to be around 0.5% in North America and Europe.[5] In the USA, the commonness has ascended from 3.2% to 5.2% in a little more than two decades from the mid-1970s to the mid-1990s. The lifetime chance is around 10– 15% in the created world, however, it can be as high as 20– 25% in the center east.[3] Nephrolithiasis is to a great extent a repetitive illness with a backslide rate of half in 5– 10 years and 75% out of 20 years,[5,6] In the vicinity of 1% and 15% of individuals all around are influenced by kidney stones eventually in their life.[4] The lifetime danger of urinary stone sickness is 12% in guys and 6% in females and the commonness of the condition is expanding, bringing about roughly 12,000 doctor's facility confirmations consistently.[3] Calcium is available in 80% of kidney stones, and most ordinarily as calcium oxalate (60%), with calcium phosphate representing 20% of stones. Around 75% of kidney stones are made out of calcium oxalate crystals.[1,3] There are about 80% of people are suffering from calcium oxalate stones.[6] Once repetitive, the consequent backslide hazard is raised and the interim between repeats is shortened.[5]

Aspects for the reappearance of stones

- Young period of beginning
- Positive family history
- Infection stones and those auxiliary to hidden therapeutic conditions—eg, hyperparathyroidism.[5]

Crystallization and consequent lithogenesis can occur with numerous solutes in the urination. Calcareous

stones are still by a wide margin the most well-known nephroliths, representing over 80% of stones.[5]

2. Risk factors for kidney stones

Different hazard factors are related to the event of the renal stone.

- ***Hypercalciuria*** Hypercalciuria is characterized as a discharge of urinary calcium surpassing 200 mg in a 24-hour accumulation or an overabundance of 4 mg calcium/kg/24 h. Hypercalciuria is the most widely recognized metabolic anomaly in patients with calcareous stones and results from different systems.[7]
- ***Hyperuricosuria*** Uric corrosive is the finished result of purine digestion and is either gotten from exogenous (dietary) sources or delivered endogenously amid cell turn over. Chronic metabolic acidosis can bring about protein digestion and in this manner expanded discharge of urate and development of kidney stones.[2]
- ***Hyperoxaluria:*** It is characterized as the urinary discharge of oxalate in an overabundance of 45 mg/day.[7]
- ***Hypocitriuria:*** It is characterized as a urinary citrate discharge of more 250 mg in 24 hours and it generally frames a solvent complex with calcium that represses the arrangement and proliferation of precious stones. It is a typical correctable reason for repetitive unadulterated calcium phosphate or brushite stones.[8]
- ***Idiopathic hypercalciuria*:** It speaks to the essential metabolic adjustment in very nearly half of patients and is characterized by levels of urinary calcium discharge in a 24-hour urine test surpassing 300 mg/day (7.5 mmoL) in males or 250 mg/day (6.25 mmoL) in females or higher than 4 mg (0.1 mmoL) per kilogram of body weight every day, paying little heed to sexual orientation and age, without hypercalcemia.[9]
- ***Genetic factors caused lithiasis*:** In genetic factors family history plays an important role as it reoccurs in another progeny. The occurrence of disease increase in male is about 2.57% and there is chances of occurrence of stones in monozygotic twins are more as compare with dizygotic twins and it is about 32.4%: 17.3% respectively.[10]

1. The genes which are helpful in making stones are endothelial growth factor, E-cadherin, vitamin-D receptor gene, and urokinase.[8]
2. OPN also helps in the formation of crystals by the means of mineralization and inflammation and this process takes place under immune cells like cytokines and macrophages.[6]

Other risk variables [8,11]

1. **Anatomic abnormalities**: medullary wipe kidney, ureteropelvic intersection stenosis, pyelo-ureteral duplication, polycystic renal sickness, and so on. Hindrance of the pelviureteral intersection. Different anomalies are:

a. Hydronephrotic renal pelvis or calices
b. Calyceal diverticulum
c. Horseshoe kidney
d. Ureterocele
e. Vesicoureteral reflux
f. Ureteral stricture
g. Tubular ectasia (medullary wipe kidney)

A. Epidemiological factors and hereditary inclination: dietary hazard factors, atmosphere, occupation, family history of stones
B. Excessive discharge of promoters of urinary crystallization: calcium (idiopathic hypercalciuria), oxalate (enteric hyperoxaluria), uric corrosive (uric corrosive hyperexcretion).
C. Abnormalities of urinary pH: renal tubular acidosis, gouty diathesis, contamination stones (struvite stones caused by urea-part living beings).
D. Reduced discharge of inhibitors of urinary crystallization: hypocitraturia.
E. Metabolic disorder and heftiness: unadulterated uric corrosive stones.
F. Low pee volume: diminished admission or expanded loss of water.
G. Hypercalcemic issue: essential hyperparathyroidism and different unsettling influences of calcium digestion.
H. Lithogenic drugs: triamterene, indinavir, sulfadiazine, uricosuric specialists.
I. Inflammatory gut ailment and other intestinal malabsorption states

Food which increments the impact of the arrangement of oxalate stones

- Fruit juices like Grape organic product juice, cranberry juice, and squeezed apple and dim colas
- Organic acids rich sustenances (oxalates) like spinach, rhubarb, nuts, and wheat bran.
- Animal protein-rich sustenances like meat, eggs and fish
- Others like vitamin C and D
- Alcohol, Lager and wine to a little degree as they contain purines High admission of salt.[12]
- Keeping away from these nourishments may help diminish the measure of oxalate in the urine.

3. Mechanism of stone formation: The main mechanism steps for formation of stones are shown in figure 1 below:

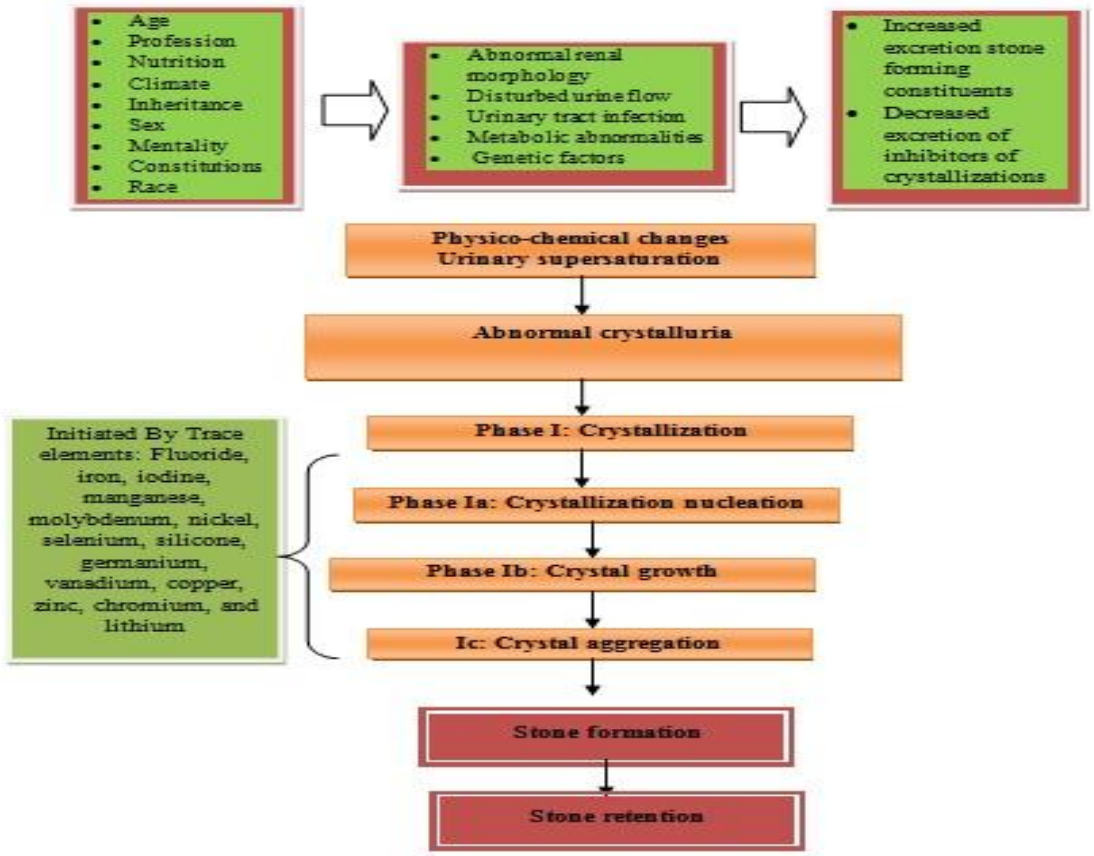

Figure 1: Mechanism of formation of stones.

- ***Crystallization:*** Crystallization known as the principal period of urinary stone development and further incorporates three stages: gem nucleation, development, and collection.[13]
- ***Nucleation:*** The nucleation is a procedure of the development of a strong stone that can be happened by homogeneous nucleation when neighborhood supersaturation permits the unconstrained association of the molecules into the fitting cross-section. Whereas heterogeneous nucleation will probably happen inside complex blends in which exceptional proteins give designs on their surface to natural atoms for the development of the underlying gem cross-section.[11]
- ***Crystal growth:*** It is a vital step in the development of stone after nucleation and during this procedure various atoms and molecules in liquid which are present in the supersaturated liquid and then begin to form clumps. Crystal growth is identified from the size and shape of the molecule along with the level of supersaturation, pH and the faults that form crystal stone.[1]
- ***Aggregation*:** Aggregation an essential advance of stone improvement, and is usually characterized as a procedure in which clusters of clusters get accumulate and shaped in bigger multicomponent particles in a free arrangement. Accumulation of particles in the arrangement is dictated by an adjust of powers, including both conglomerating and disaggregating impacts. Little interparticle separations increment appealing powers and support molecule aggregation. The procedure of crystallization is impacted by a few promoters and inhibitors and in addition some morphoanatomic, dietary and ecological elements. Along with the small number of metals like fluoride, iron, iodine, manganese, molybdenum, nickel, selenium, silicon, germanium, vanadium, copper, zinc, chromium, and lithium are present to start the procedure of crystallization.[14]
- ***Stone retention***: After the crystallization procedure is finished, the maintenance of urinary stones inside the urinary framework is an essential advance in the improvement of the infection. The urothelium is there for providing stone adherence. Be that as it may, synthetic or mechanical urothelial harm may advance precious stone binding and aggregation. Up until now for retention of stones, there are 2 hypotheses which are free particles and fixed particles. As indicated by the free particle hypothesis, the procedure of nucleation happens altogether in the tubular lumen. As crystallized mass displaced through the renal tubules, quickly total and develop sufficiently substantial to stall out inside the tubular lumen. As per fixed particle theory, the mass of crystals gets stick to a stable point like renal epithelial cells or Randall's plaque. The four different possible modes of stone retention have been identified in the fixed particle hypothesis, namely:
  - Development over white (Randall's) interstitial hydroxyapatite plaque
  - Development over Bellini channel plugs

- Arrangement of small scale liths inside internal medullary collecting ducts
- Arrangement in free arrangement inside the calyces or renal gathering framework.[15]

4. Symptoms of kidney stones: The various symptoms are shown in the table 1 below:

Table 1: Symptoms of kidney stones.

General symptoms	Systemic symptoms	Non-systemic symptoms
Pain, haematuria, dysuria, strangury.[16]	The restless motion of body, nausea, chills, and infection, pyelonephritis and acute renal failure.[6,16]	Incidental stones.[16]

5. Existing treatment of kidney stones using different plants/ drugs in medicine system

The various medicine system are there which are used for the treatment of the kidney stones and the drug and plant extracts used for the curing calcium oxalate kidney stones are shown in table 2 below:

Table 2: Different plants/drugs used for kidney stone treatment in various medicine system.

Sr.no	Medicine system	Plants/Drugs used
1.	Allopathic system	Allopurinol, Zonisamide, Etidronate disodium.[1]
2.	Ayurvedic system	*Alhagi mannifera, Ocimum, Zingiber Officinale, Ficus carica, Nothosasrva brachiata, Homonoia riparia.*[1,17]
3.	Unani system	*Dolichos biflorus, Carthamus tinctorius, Daucus carota linn, Pisum sativum, Foeniculum vulgare, Tribulus terrestris.*[8,20]

6. Some herbal plants currently evaluated as antiurolithiatic drugs in-vivo studies in different counties

There are so many herbal extracts which are being evaluated as the source of curing the kidney stones. Some of the examples are shown in the table 3 below which are evaluated as the therapy for kidney stones in different countries.

Table 3: Different plants used in different countries for treating kidney stones.

Sr. no.	Country	Plant used
1.	India	*Sesbania grandiflora, Aerva lanata, Moringa oleifer, Rotula aquatic peltata, Bergenia ligulata, Tribulus terrestris.*[21,22]
2.	Japan	*Alisma orientale, Quercus salicina Blume, Costus spiralis.*[21]
3.	Mexico	*Randia echinocarpa Sesse, Raphanus sativus.*[23,24]
4.	China	*Bryophyllum pinnatum.*[22]
5.	Others	*Rubia tinctorum, Citrus limon, Costus spiralis.*[22]

7. Different animal models used for kidney stone induction studied in this review

The induction of kidney stones is done with different types of methods. For inducing calcium oxalate crystals the most common methods are as under:

- Ethylene glycol (EG) and ammonium chloride
- Diet-induced urolithiasis
- Sodium oxalate

Ethylene glycol: It is chemically known as Ethan-di-ol and is mostly used as a solvent and automobile antifreeze agent.[25] Ethylene glycol and ammonium chloride can be used in combination as antiurolithiatic agents.[13] This method is most preferable because it led to precipitation of the calcium and phosphorus and the calcium oxalate crystals are formed as a result. The drug when combined with the ammonium chloride it boosts the production of the calcium oxalate formation and also enhances the acidosis.[25] The compensation of using ethylene glycol is the easy availability of the solvent, target only the kidneys and get metabolized in the body. The disadvantage of using this solvent is cellular damage and nephrotoxicity.[25]

Mechanism of action: The mechanism starts from the absorption of EG in the liver rapidly by enzymes like alcohol dehydrogenase and aldehyde dehydrogenase to form glycol acid. The formed acid is then oxidized to glyoxylic acid and further oxidized to oxalic acid via enzyme glycolate oxidase or glycolate lactate dehydrogenase and those promoting to Hyperoxaluria. It is a major cause of the formation of lithiasis in the kidney.[25,26]

- ***Diet-induced model***: The lithiasis can be caused by using a modified diet in the animal model just by altering the dietary contents with the stone inducing components.[26,27] The calcium oxalate stones can be

easily formed by elevating the levels of the calcium via diets and for that purpose one of the best sources is ethylene glycol combined with lactose and consumed it with lactose.[228,29] The diet rich with protein, sucrose, and fats also causes oxalate stones. The advantages of using this method are stable deposition of the crystal growth and no toxicity in the kidney.[30]

- ***Induction of lithiasis in rats by using sodium oxalate*:** The lithiasis caused by elevating the levels of the urea in the kidney. The oxalate crystals are formed is evaluated by using sodium oxalate animal models. The sodium oxalate can be estimated in urine and the calcium deposition leads to the formation of calcium oxalate stones. The advantages of the model are the stone formation is for a small period of time and it is a more stable model.[25,31,32]

Table 4: In-vivo study of different plants extracts using different animal models with purposed mechanism.

Sr. No.	Name of plant	Experimental Model	Treatment	Result of study	Proposed Mechanisms	References
1.	Fucoxanthin from brown seaweed	EG induced in albino Wistar rats	Aqueous extract	Reduction in stone, phosphorous and magnesium levels at 80 mg/kg dose	Antioxidant	[37]
2.	*Bryophyllum pinnatum*	EG induced in Male albino rats	Ethanolic and petroleum ether extract of 8.76%	Reduction in kidney stones	Antioxidant	[38]
3.	*Cannabis sativa*	EG induced in adult Wistar rats	Aqueous extract of 100 mg and 200 mg	Reduction in crystallization size of stone	Antioxidant	[39]
4.	*Triclisia gilletii*	EG induced in male wistar rats	Aqueous-ethanolic extract of 17.21% w/w	Retard the oxalate and calcium aggregate formation	Antioxidant	[40]
5.	*Curcuma zedoaria*	EG induced in male albino Wistar rats	Ethyl acetate extract of o pulp of 200 mg	Retard the oxalate formation	Antioxidant and reduces the oxalate formation by enhances nitric oxide	[31]
6.	Citrullus Lanatus	EG and ammonium chloride	Ethanolic extract	Prevent the growth of callus and inflammation	Antioxidant	[41]
7.	*Vernonia cinere*	Ethylene Glycol (EG) and ammonium chloride in Wistar rats	Hydro-ethanolic extract of 100, 300 and 500 mg/kg,	Showed a reduction in stone size and reduction in oxidative stress at all doses	Antioxidant	[34]
8.	*Desmodium styracifolium*	5% w/w hydroxy-l-proline (HLP)	Ethanolic extract of HLP 100, 400 mg/kg	Showed reduction in stone size at HLP 400 mg	Act as antioxidant, Urine alkalinizing agent and Inhibiting MCP-1, OPN, and TGF-β expression	[42]
9.	*Chenopodium album*	EG in adult Wistar rats	Hydroalcoholic extract	Significantly reduced urinary and plasma levels of calcium, phosphorus, urea, uric acid, and creatinine levels, reduced renal tissue oxalate levels and deposition.	Reduction in crystallization and promote stone dissolution.	[43]
10.	*Biophytum sensitivum*	EG–ammonium chloride in Male Wistar albino rats	70% v/v methanol in water of 100, 200 and 400 mg/kg	Reduced kidney calcium, oxalate and phosphate levels, reduced lipid peroxidation and improved histology in dose-dependent effect	Act as diuretic, maintain the level of, reduces the excretion of phosphate, restore the amount of mangnessium, reduce hyperoxalurea and serum level	[44]

11.	*Launaea procumbens*	EG in male Wistar albino rats.	Methanolic extract 150 and 300 mg/kg	300 mg/kg is the effective dose for reduction of urinary calcium, oxalate and number of oxalate crystals. Restored magnesium levels, decrease the excretion of protein	Act by antioxidant properties and increase the NO bioavailabity through cGMP pathway.	[45]
12.	*Adiantum capillus*	0.75% EG and 1% ammonium chloride in male sprague rats	Hydroalcholic extract of 127.6mg/kg and 255.2mg/kg	Significant reduction in number of crystals, calcium, phosphate and urea and normalized histoarchitecture of kidneys	Act as anticalciuric, antioxidant, anti-inflammatory	[46]
13.	*Foeniculum vulgare and Cymbopogon proximus*	Sodium oxalate in Male Wistar rats	Aqueous extracts 1.47 and 1.20 mg/24 h	Normalized urine oxalate, calcium, protein as compared to the negative control, urinary marker enzyme excretion is reduced, reduced lipid peroxidation, preserved normal morphology of kidneys.	Beverages reduced levels of urinary risk factors for calcium oxalate stone formation, prevented renal membrane damage and prevented renal injury via free radical quenching, promoted dieresis and preserved normal renal histoarchitecture	[20]
14.	*Leea macrophylla*	EG in male wistar albino rats	ethanolic extract of 500mg/kg for therapeutic dose and 0.75,1.5,2.5 and 3.5g/kg body weight	Urinary calcium, inorganic phosphate, oxalate, magnesium and creatinine and renal morphology was normalized	Significanlty reduced the stone deposition and stone growth in female rats as compared to male rats and facilitating its excretion	[47]
15.	*Alcea rosea*	EG in Male Wistar rats	Hydroalcoholic extract of 170 mg/kg,	Showed reduction in stone size at all doses	Act by inhibiting hyperoxaluria, diuretic, antioxidant, antibacterial action	[48]
16.	*Punica granatum*	EG in male albino rats of Wistar strain	Extract of *P. gratum*100, 200 and 400 mg/kg	400 mg/Kg dose was effective in the reduction of stone sizes, urinary calcium, oxalate, urea, uric acid and phosphate levels	Act as Anti-inflammatory and antioxidant	[31]
17.	*Persea americana Mill*	0.75% EG and 2% ammonium chloride in male Sprague Dawley	Ethanolic extract of 100 and 300 mg/kg bw	7% reduction in stones with Avogadro leaves 100 mg/kg bw and 1% by 300 mg/kg bw.	Acting as an anti-inflammatory by inhibiting leukotriene synthesis, prevention of histamine release,inhibition of neutrofil degranulation and Antioxidant	[49]
18.	*Orthosiphon stamineus*	EG and ammonium chloride in Sprague-Dawley male rats	Ethanolic extract of 80mg/kg and 160 mg/kg	Both doses are effective and prophylactic by reducing aggregation of calcium oxalate.	Regulate OPN expression	[50]
19.	*Desmodium styracifolium and Pyrrosiae*	5% Ammonium oxalate male Wistar rats	275, 550 and 1,100 mg/kg for Ds and 150, 300	Effective dose in Pp group 600 mg/kg and in Ds dose is 550 and	Acting as diuretic, increasing calcium oxalate output,	[51]

	petiolosa		and 600 mg/kg for Pp	1100 mg/kg	antioxidant	
20.	*Flos carthami*	EG in male Sprague–Dawley rats	300 mg/day and 600 and 1,200 mg/day to examine the high-dose response.	Effective doses 600mg and 1200 mg/day, reduced calcium oxalate deposition and bleeding tendency	The exact mechanism of action is unknown but there is decrease in size of stones	[52]
21.	*Asparagus racemosus*	EG and Ammonium chloride in albino rats	ethanolic extract 800 and 1600 mg/ kg	Both doses reduced urine concentrations of calcium, phosphorous, urea and creatinine with improvement in histopathology.	Act as diuretic by inhibiting supersaturation, antioxidant, antibacterial	[53]
22.	*Bergenia ciliata (BC)*	EG in female Wistar rats	Hydroalcoholic (70% methanol) of BCE in 150 and 300 mg/Kg BW	Effective dose , 300 mg/Kg inhibited nucleation, and aggregation of calcium oxalate monohydrate crystals.	Acting as anticalciuric, anti-inflammatory	[54]
23.	*Origanum vulgare*	0.75% EG and 1% Ammonium chloride in wistar rats	aqueous-methanolic extract 20-60 mg/kg and log doses 10 and 30 mg/kg	Effective dose reversed crystalluria, oxaluria, raised serum urea and creatinine levels and crystal deposition and also inhibited nucleation and aggregation	Acting as diuretic, antioxidant, antispasmodic	[55]
24.	*Nigella sativa*	EG-induced in male wistar rats	aqueous–ethanolic extract of N butanol of 250 mg/kg	N-butanol fraction reduced number and size of kidney calcium oxalate deposits.	Acting as anti inflammatory, antioxidant	[56]
25.	*Pergularia daemia*	EG in Wistar rats and Swiss albino mice	Hydro-Alcoholic extract of 400 mg/kg	Significantly reduced the stone forming urine constituent and retarded retention in bladder.	Act as diuretic and antioxidant	[57]
26.	*Orthosiphon grandiflorus, Hibiscus sabdariffa and Phyllanthus amarus*	3% glycolate diet in aqueous extract	Aqueous extract of 3.5 mg tablet	Significantly increase urinary citrate levels, reduced calcium oxalate crystal deposition, renal tissue calcium levels.	Acting as diuretic, antioxidant and Citraturic	[29]
27.	*Urtica dentata*	1.25% EG and 1% ammonium chloride in male Sprague-Dawley rats	Ethanolic extract of 75 mg/kg	Effective dose promoted flushing of renal stone with renal function protection.	Acting as anti-inflammatory and diuretic	[58]
28.	*Helichrysum plicatum*	EG and ammonium chloride in Sprague Dawley rats	Hydroalcoholic extract of 125, 250 and 500 mg/kg	500 mg/kg dose rats were normal, no intratubular crystal depositions and histopathological changes in all urolithiasis.	Acting as antioxidant activity	[59]

8. Ayurvedic alternatives *v/s* allopathic treatments: Benefits and scope

From ancient times medicinal plants are used to treat human diseases. In the developing countries about 80% of the population of the world using herbal plants for their treatment as they are used widely as medicines and also easily available.[20] Due to disappointment with modern medicines, Ayurvedic therapy and the use of

herbal plants are becoming become more observable for the treatment of diseases.[17] The therapeutic value of Ayurvedic drugs are being there but in some cases, it is not there because research on those plants is not being done yet.[15] Just like synthetic drugs that are being tested in clinical trials, herbals plants also be tested at the clinical level to check their efficacy but apart from this, there is a presence of logical and methodological problems.[33] As per WHO traditional herbal plants which are present for more than a hundred years have their therapeutical practices as they are still in use in the era of modern drugs.[33] Ayurveda is popular due to the following reasons like a traditional system, tested over a long period, no harmful chemical compound is added in the herbal formulations.[34]

Today, the people are changing their opinions about herbal plants and medicines and the affidavit of this is the usage of the herbal drug is also being raised in the world as well because the people of the world are getting irritated from the modern system of medicines.[35] due to following reasons like the high cost of medicines, increased side effects along with safety and efficacy issues, for chronic diseases the treatment is not always successful and relief is based on symptoms only.[20,33,36]

9. The in-vitro studies done on the animal model for trating calcium oxalate crystals using different herbal extract

The different herbal extracts used to cure calcium oxalate kidney stones along with experimental model, treatment dose along with proposed mechanism is shown in table below. The table consist of various mechanism of action of the plant extracts along with result of the study. The in-vivo study was conducted on rats and mice and the experimental model is also explained table.

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