IJBPAS, December, 2023, 12(12): 5468-5481

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

ROLE OF PHYTOCONSTITUENTS IN THE MANAGEMENT OF UROLITHIASIS: A REVIEW

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Received 19th Nov. 2022; Revised 16th Dec. 2022; Accepted 1st April 2023; Available online 1st Dec. 2023

https://doi.org/10.31032/IJBPAS/2023/12.12.7601

ABSTRACT

Kidney stones or urolithiasis is a worldwide medical challenge to the urinary system. It is a multifactorial painful phenomenon that occurs due to various physiochemical alterations in the urinary tract like the imbalance between stone promoter and inhibitors, supersaturation, and many more. General causes of urolithiasis are insufficient urinary effluent, foreign matter in the urinary tract, bacterial infections, a diet rich in oxalates and calcium, vitamin A inadequacy, surplus of vitamin D and various metabolic ailments like hyperthyroidism, cystinuria, intestinal dysfunction and others. The recurrence rate of urolithiasis is also very high. Medicinal plants are always useful in the management of a variety of metabolic ailments because of the presence of their potential phytoconstituents. Several plants and phytoconstituents have been reported for their action against urolithiasis, So the current review article explains the role of promising potential active phytoconstituents in the treatment of urolithiasis as well as have a brief idea about medicinal plants that have important phytoconstituents but still have not been assessed for their anti-urolithiatic action. The current review covers the pathophysiology of stone formation along with the various approaches through which a kidney stone can be targeted.

Keywords: Urolithiasis, Kidney stone, Berberine, Chemical constituents, Triterpenoids

INTRODUCTION

Urolithiasis or kidney stone is the oldest, 3rd most common painful urinary problem **[1]**. In general, the risk of urolithiasis occurrences is about 10-25% with a high reoccurrence rate **[2]**. Stones can be classified based on their chemical composition, size, location, pathogenesis, recurrence risk factor and X-ray characteristics. The most common stone is calcium oxalate stone. In most cases, hyperoxaluria is the condition responsible for the formation of CaOx stone **[3, 4]**. A large number of patients who have larger renal stones are required to go through extensive surgical procedures like lithotripsy, ureteroscopy, shock wave lithotripsy and percutaneous nephrolithotomy. However, the majority of these surgical procedures have adverse effects, which has generated great interest in alternative therapies in this field **[5]**. Plants belonging to the 'Pashanabheda' category are said to be highly important in the treatment of urolithiasis in the Indian Ayurvedic medicine system. Other than this category of plant other plants also have been scientifically assessed for their anti-urolithiatic potential. In this era still, many peoples prefer traditional medicine to fulfil their primary healthcare needs. Various phytoconstituents are pharmacologically screened for the development of novel agents with fewer side effects. So, the present review article explains the role of promising potential active phytoconstituents in the treatment of urolithiasis as well as have a brief idea about herbal plants that have important phytoconstituents but still have not been assessed for their anti-urolithiatic action. The current review is also aimed to collect information on various approaches through which a kidney stone can be targeted.

PATHOPHYSIOLOGY

- Urolithiasis is a complex biological action in which minerals get accumulated in the kidney and its definite pathophysiology has not been fully clarified yet. Stone promoters and stone inhibitors play a vital role in urolithiasis. Stone promoters are those that help to promote the formation and growth of stones (like the low volume of urine, acidic urine and excess oxalate, calcium, phosphate, urate, and cystine in the urine) and stone inhibitors which play role in the inhibition of stones (like calgranulin protein, Tamm-Horsfall protein, glycosaminoglycans, osteopontin-uropontin, nephrocalcin, prothrombin F1 peptide, bikunin protein, citrate, magnesium, uromodulin, pyrophosphate etc. **[6, 7]**. A balance between these two is necessary when it gets disturbed due to any circumstances, the solidification of chemicals and minerals into salt crystals gets started which leads to stone formation **[8]**. In normal conditions, these crystals

pass through urine without producing any harm **[9]**. However occasionally, if they become large enough so that they cannot be eliminated naturally then they may serve as a nucleus for the deposition of more crystals, and this leads to the formation of future stones **[10, 11]**. A variety of urinary constituents may affect its composition. For example, citrate and magnesium make soluble complexes with calcium and oxalate, respectively, by doing this they reduce free ions and so which reduces the relative supersaturation level of calcium oxalate in urine and tubular fluid **[12]**. Urolithiasis is a multi-staged condition that includes urine saturation, supersaturation, nucleation, crystal development, aggregation of crystals, crystal retention, and, finally, stone formation for a better understanding of kidney stone pathogenesis, each stage is described as follows:

Initiation of stone formation: The interaction between crystals and renal tubular epithelial cells, including crystal adherence or endocytosis by cells, has lately been highlighted by some researchers as a key element in stone production **[13]**. It is thought to occur by either a free particle or a fixed particle theory **[14]**. Stone may get fixed to the urothelium for further growth. Another theory says that stone formation starts in the papilla of the kidney, on which either oxalate or calcium phosphate crystals begin to deposit **[11]**. According to Randall plaque-like lesions are found in the papillae. These lesions form a nucleus (named Randall plaque) on these calcium oxalate stones that develop and grow through the nucleation process **[15]**. Dr Khan recently proposed a theory for the pathogenesis of Randall's plaque, stating that abnormal urinary conditions such as hypercalciuria, hyperoxaluria, and hypocitraturia, as well as renal stress or trauma, cause renal epithelial cells to transform into an osteoblastic phenotype, with increased production of osteopontin, decreased crystallisation inhibitors, and increased matrix vesicles, which support crystal nucleation **[16]**.

Crystal Nucleation: If any ulceration or damage is present in the calculi of the kidney, it may possible that pus may get accumulated there and then get solidified so that it can act as a nucleus or nidus for the formation of stones **[17]**.

Crystal Growth*:* It will occur after the nidus has adhered to the urothelium. The formed nidus acts as a nucleus for subsequent stone growth **[18]**. Crystals of urine stick around the nidus and form a small hard mass of stone. On the matrix-coated surface, it is performed through the aggregation of pre-existing crystals or subsequent nucleation of crystals.

Crystal Aggregation*:* it is the process through which a little hard mass of a crystal

in solution clings together to produce a bigger stone **[19]**.

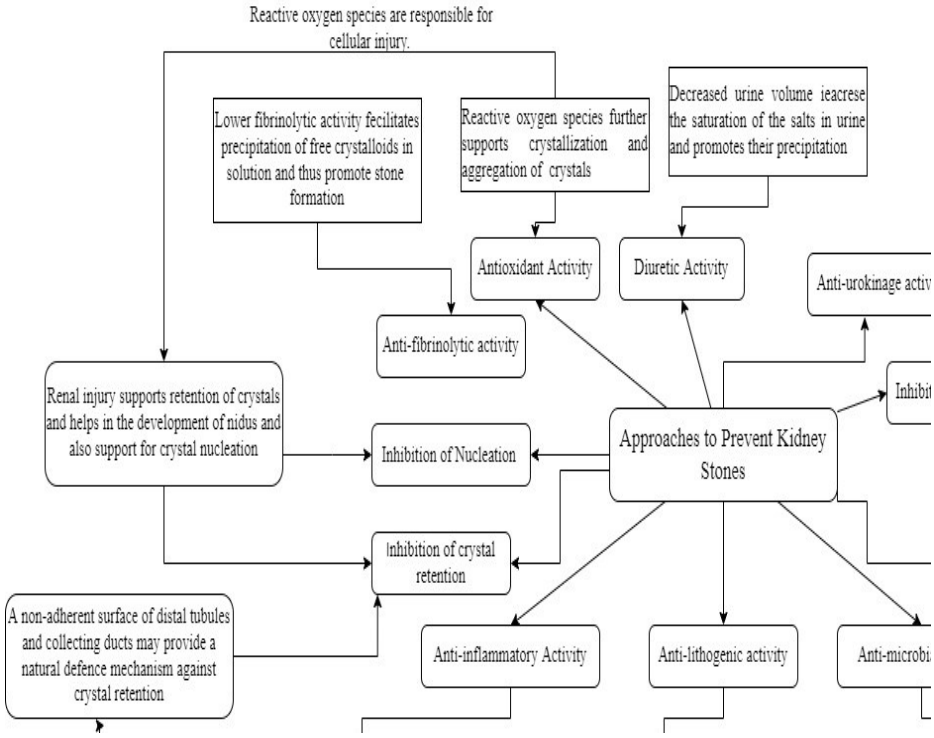
Crystal-Cell Interaction*:* It refers to the attachment of growing crystals to the epithelial lining of the renal tubule. After a stone event, urothelial injury and healing may boost the surface expression of these molecules, allowing for more crystal attachment and stone development **[18]**. Although there are various theories to explain the aetiology of renal calculi, the exact sequence of events that leads to the production of kidney stones is still unknown.

MANAGEMENT OF UROLITHIASIS

The top treatment priority of urolithiasis is to help pass or remove all of the stones in minimum harmful ways. To achieve this goal some medications known as medical expulsive therapy and least invasive modalities like nutritional modifications and surgery are the main ways **[20-22]**. It is possible to expel the small size renal stones by inculcating more water in a regular lifestyle. Which increases the volume of urine which lead to inhibiting urinary saturation and diluting the concentration of promoters. In the case of hyperoxaluria, a diet with low oxalate levels, animal protein and a diet with high calcium, and citrate intake is recommended **[23, 24]**. If the size of stones is larger than 5mm then the various surgical procedure suggested **[25-27]**. Although they are effective in stone removal but not free of risks and are costlier too **[28]**. Certain medications are also useful which show their effectiveness in stone removal like thiazides, potassium citrate, allopurinol etc. Now with novel technical advancements, new treatment protocols like citrate therapy for recurrent calcium renal stones have become common over the last decade **[29, 30]**. Medical management of renal stones is either costly or has various unwanted effects. Thus, there is increasing interest in the public, day by day in herbal medicine, especially in kidney stone management. Various studies prove that many medicinal plants are used in the treatment of urolithiasis since ancient periods in India, even before the invention of modern treatment methods and drugs. From the literature, it is clear that herbal plants and their extracts are capable to manage various steps of the crystallization process.

In **Flow chart 1** approaches are summarised which are useful to understand the treatment approach of urolithiasis:

Various studies all over the world have reported that many herbal plants have been applied as a therapeutic to urolithiasis, some are shown in **Table 1**.



Flow Chart 1: Treatment Approach of Urolithiasis

Table 1: List of plants that have been used for the treatment of urolithiasis

Name of plant, Family, Part, Extract	Proposed mechanism against urolithiasis	Study design *In vivo/In vitro*	Animal and dose	References
***Ononis Spinosa*, Fabaceae, Root**	**It may have litholytic, diuretic and anti-inflammatory effect**		**-**	**Bashan *et. al.*, 2020 [31]**
***Ananas nanus*, Bromeliaceae and others**	**Inhibit nucleation of calcium oxalate, Disintegrate the mucoproteins, Decrease the level of stone promoter solutes**	***In vitro***	**-**	**Sairi *et. al.*, 2019 [32]**
***Cinnamomum zeylanicum*, Lauraceae, Bark, Hydroalcoholic**	**Decrease crystallization by disaggregating the suspension of mucoprotein**		**4, 8 and 10 mg/ml**	**Zaki *et. al.*, 2019 [33]**
***Daucus carota*, Apiaceae, Roots, Hydroethanolic extract**	**Anticrystallization ability, Improve urine and serum biochemistry along with renal cellularity**	**CO induced urolithiasis *In vivo***	**Wistar rats 200 and 400 mg/kg**	**Bawari *et. al.*, 2018[34]**
***Duranta erecta*, Verbenaceae, Leaves, Methanolic extract**	**Decrease hyperoxaluria, Inhibit calcium oxalate crystallization**	**Sodium oxalate *In vitro, In vivo***	**Wistar rats 50 mg/kg**	**Agawane et. al., 2018[35]**
***Pedalium murex*, Pedaliaceae, Leaves, Ethyl acetate extract**	**Decreases activity of urease enzyme increases urine pH, Inhibit crystal formation**	**Ethyl acetate induced urolithiasis *Invitro, In vivo***	**Wistar rats 300 mg/kg**	**Kaleeswaran *et. al.*, 2018[36]**
***Piper cubeba*, Piperaceae, Fruit, Hydroalcoholic extract**	**Possibly due to the presence of flavonoid and alkaloids**	**CO induced urolithiasis *In vivo***	**Sprague rats 35 and 60 mg/kg**	**Bano *et. al.*, 2018[37]**
***Terminalia arjuna*, Combretaceae, Bark, Aqueous extract**	**Inhibit interaction of CaOx crystals with epithelial cells of the kidney, thus preventing kidney cells to damage by CaOx crystals**		**Oxalate injured cells 40 µg/mL**	**Mittal *et. al.*, 2018[38]**

***Trigonella foenum-graecum*, Fabaceae, Seed, Aqueous extract**	**Formation of complexes of polyphenols or flavonoids (present in *T. foenum-graecum*) with stones**	***In vitro***	**-**	**Yachi *et. al.*, 2018[39]**
***Aerva lanata*, Amarantheceae, Leaves**	**Decrease quantity of stones, Decrease creatinine and blood urea nitrogen and show diuretic activity**	**CO induced urolithiasis *In vivo***	**Wistar rats 2 mg/kg**	**Dinnimath et.al., 2017[40]**
***Ensetesuperbum*, Musaceae, Chloroform extract**	**Decrease levels of Ca^{2+}, uric acid, and creatinine in urine and serum**	**EG induced urolithiasis *In vitro, In vivo***	**Wistar rats 100, 200,400 mg/kg**	**Sethiya et. al., 2017[41]**
***Phlogacanthusthyrsi formis*, Acanthaceae, Flowers, Aqueous extract**	**Form a complex with Mg^{2+} and limit their availability for crystal growth, Inhibit nucleation of crystals**	**Chemically induced urolithiasis *In vitro, In vivo***	**Wistar rats. 200 mg/kg**	**Das et. al., 2017[42]**
***Vernonia cinerea*, Asteraceae, Whole plant**	**Biochemical abnormalities were repaired in the urine, serum, and kidney tissue homogenates**	**CO induced urolithiasis *In vivo***	**Wistar rats 100,300,500 mg/kg**	**Goyal *et. al*., 2017[43]**
***Chenopodium album*, Chenopodiaceae, Leaves, Ethanolic & aqueous extract**	**Inhibit crystal growth**	**EG induced urolithiasis *In vivo***	**Wistar rats 100, 200, 400 mg/kg**	**Sikarwar *et. al.*, 2017[44]**
***Helichrysum*, Asteraceae, Flowers, Infusion**	**Urine uric acid and oxalate levels were reduced, while citrate levels were increased**	**Sodium Oxalate Induced Urolithiasis**	**Wistar rats 125,156 mg/kg**	**Onaran *et. al*., 2016[45]**
***Peucedanumgrande*, Hydroalcoholic extract**	**Decrease CaOx crystals in the urine, Decreases calcium, phosphorus, creatinine, urea, sodium level in urine, Increase urine volume**	**EG induced urolithiasis *In vivo***	**Sprague rats 56, 97 mg/kg**	**Kumar *et. al*., 2016[46]**

CHEMICAL CONSTITUENTS USED IN ANTI-UROLITHIATIC MODELS: Plants and their phytoconstituents were reported for their protective action against urolithiasis. Following are the various phytoconstituents reported as having anti-urolithiatic potential.

Berberine: Bashir *et al.,* reported in their studies that *Berberis vulgaris* root bark extract has anti-urolithiatic potential, possibly mediating their effect by inhibiting the crystallization process by their antioxidant activity **[47]**. In various research articles, it is reported that oxidative stress has been increased during kidney stone formation and berberine was reported as a very good antioxidant. As a result, berberine could be a promising target for kidney stone treatment **[48]**. It is found as a primary component in a variety of plants including *Berberis aquifolium, Berberis aristata Berberis vulgaris, Tinospora cordifolia, Mahonia Argemone, Mexicana aquifolium, Tinospora cordifolia* and these plants have been already reported for their anti-urolithiatic potential. There are other plants also that are reported as a good source of berberine and still not assessed for their anti-urolithiatic potential like *Hydrastis canadensis, Coptis chinensis, Phellodendron, and Greater celandine. Eschscholzia californica, Xanthorhiza simplicissima, Coelocline polycarpa, Papaver dubium, Papaver hybridum, Rollinia deliciosa, Xanthorhiza simplicissima, Xylopia macrocarpa* **[49,**

50]. These plants are a future candidate for anti-urolithiatic activity.

Quercetin: Various research activities showed a potential effect of quercetin against urolithiasis. It reduces stone formation due to its diuretic, and antioxidant effects and by lowering oxalate excretion, and nucleation. It reduces the development of crystals, as well as boosting magnesium levels and decreasing crystal-cell binding **[51-54]**. It is found in various plants like *Morus alba, Camellia sinensis, Moringa oleifera, Centella asiatica, Hypericum hircinum, Hypericum perforatum, Apium graveolens, Brassica oleracea var, Coriandrum sativum, Lactuca sativa, Nasturtium officinale, Asparagus officinalis, Capparis spinosa, Prunus domestica, Prunus avium, Malus domestica, Solanum lycopersicum, Vaccinium oxycoccus, Allium cepa, Allium fistulosum* **[36]**. Some of above-suggested plants could give excellent results in urolithiasis reduction.

Triterpenoids: Oleanolic acid, lupeol, ursolic acid, a-amyrin, b-amyrin and betulinic acid are common triterpenoids found in plants. The root bark of plants like *Crataeva nurvala*, *Crataeva magna*, *L. prostrata* and *M. philippensis* has been proven to be effective in the treatment of urolithiasis. [55] Anti-urolithiatic effect of these plants may be attributed to the presence of lupeol, betulin, α-amyrin, β-sitosterol, etc. **[56]**. Plasma lipoxide levels are reduced by maslinic and ursolic acids. Lupeol and its derivatives were reported effective in inflammation, microbial infection, ageing, and angiogenesis and also effective in reducing the level of cholesterol. Lupeol also lowers calcium-oxalate levels and has anti-free radical effects, as well as decreasing cadmium levels in the kidney **[57, 58]**. *N. binaludensis and Ficus pseudopalma* have α-amyrin, β-amyrin and lupeol reported for their anti-urolithiatic effect.[59] Results suggested that urolithiasis effect is produced due to the inhibition of creatinine and level of oxalate in urine **[60]**. Triterpenes distributed in various plants like *Aloe vera, Arctostaphylos uva-ursi, Aegle marmelos, Betula alba, Bacopa monniera, Calendula officinalis, Centella asiatica, Cornus officinalis, Cornus mas, Malus domestica, Eriobotrya japonica, Nerium oleander, Melissa officinalis, Ocimum basilicum, Olea europeae, Lantana Camara, Origanum majorana, Pimpinella anisum, Gymnema inodorum, Pyrus communis, Thymus vulgaris* etc plants reported for their potential against anti-urolithiatic activity. So those plants that have these triterpenes in a good amount will be a good target against anti-urolithiatic activity like *Ligusticum lucidum, Lantana camara Sorbus commixta, Acacia mellifera, Fagus hayatae*

etc. these plants are scientifically assessed for their anti-urolithiatic effect. Lupeol should be researched clinically to see its potential against kidney stones.

Gallotannin: they are strong antioxidants in nature. It significantly reduced crystal formation and binding to renal epithelial cells. It significantly reduced oxalate-induced mRNA expression of monocyte chemoattractant protein 1, osteopontin, nicotinamide adenine dinucleotide phosphate oxidase, subunit p22phox, and p47phox on renal epithelial cells. Gallotannin boosted the activity of the antioxidant enzyme superoxide dismutase in response to oxalate **[61]**. It is also demonstrated by Several laboratories that tannins exert potent anti-inflammatory effects also. *Mangifera indica, Betula pubescens, Rhus coriaria, Punica granatum* reduced nitric oxide synthase, p38-mitogene-activated protein kinase, and p65-nuclear factor-kB expression on hyperoxaluria-induced oxidative stress and stone formation in rat kidneys, inhibiting renal tubular cell damage and oxidative stress caused by oxalate crystals **[58]**.

Curcumin: Curcumin is a yellow-orange dye obtained from the powdered root of *Curcuma longa*. Curcumin's antibacterial activity against periodontopathic bacteria was tested in periodontal tissues by Izui *et al.* Periodontopathic bacteria cause chronic periodontitis, which is an inflammatory disease. It confirms that it has good antibacterial as well as good anti-inflammatory activity.[61] Rahman *et al.,* confirmed the preventive curative potential of curcumin on ethylene glycol-induced urolithiasis through their experimental work. As a result of its effect on the early phases of stone production, curcumin may be effective in preventing the recurrence of urolithiasis **[62]**.

Catechin & Rutin: both are components of green tea. Green tea has been shown to have anti-inflammatory and antioxidant properties in both *in-vivo* and *in-vitro* tests. Various plants like *Arrabidaea brachypoda Bureau, Rhizophora mangle, Camellia sinensis, Actinidia deliciosa, and Malus pumila Mill* have catechin and rutin. Zhai *et al* discovered that calcium mono-oxalate crystals increase mitochondrial membrane potential and the production of superoxide dismutase, 4-hydroxynonenal, cytochrome c, and cleaved caspase 3 in NRK-52E cells. *In vivo* experiments, catechin reduces these enzymes. Also, they have done the *in-vitro* study and concluded that renal calcium crystallization is inhibited. Possibly by decreasing the expression of osteopontin in renal tubular cells **[63]**.

CONCLUSION:

Urolithiasis is a multifaceted urological condition. The physical process of stone creation is quite complicated. The status of urine saturation, crystal development,

aggregation, and retention, as well as crystal formation inhibitors and promoters, are still being debated. Taken together, it is suggested that the use of dietary polyphenols, pentacyclic triterpenoids, saponins, tannins, flavonoids, isoquinoline alkaloids and many more could be useful for the treatment of urolithiasis. There could be several mechanisms at work behind the protective effect of the constituents of the plants indicated above. The benefits of medicinal plants are widely recognised, including lower toxicity, safety, effectiveness, low cost, low disease recurrence rate, and ease of access. The present review conveys information about medicinal plants which have promising research prospects in the field of kidney stones. Plant extracts have been demonstrated to have anti-urolithiatic actions by changing the ionic composition of urine, lowering calcium ion concentrations, and increasing magnesium and citrate excretion. Limited research suggests that herbal medications can help with urolithiasis through a variety of mechanisms. The present paper provides information regarding potential medicinal plants and phytoconstituents used in the management of urolithiasis to develop a new drug to overcome the various disadvantages faced by the wide range of population nowadays and get relieved from the disease. To acquire more definite results, more preclinical and clinical research is needed to establish the efficacy and safety of these phytoconstituents in patients with kidney stones.

REFERENCES:

[1] Santhoshi B, Chidrawar VR, Rao VU, A Brief Review on the Potential Medicinal Plants and Screening Models of Urolithiasis, Int J Appl. 2015; 6:37-45.

[2] Patankar SB, Mujumdar AM, Bernard F, Supriya P, Safety and Efficacy of An Herbal Formulation in Patients with Renal Calculi-A 28 Week, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study, J Ayurveda Integr Med. 2020; 11:62.

[3] Gupta S, Kanwar SS, Kidney Stones: Mechanism of Formation, Pathogenesis and Possible Treatments, J Biomol Biochem. 2018; 2:1-5.

[4] Ahmed S, Hasan MM, Khan H, Mahmood ZA, Patel S, The Mechanistic Insight of Polyphenols in Calcium Oxalate Urolithiasis Mitigation, Biomed Pharmacother. 2018; 106:1292-1299.

[5] Evan AP, Physiopathology and Etiology of Stone Formation in the Kidney and the Urinary Tract, Pediatr Nephrol. 2010; 25:831-841.

[6] Halbritter J, Genetics of Kidney Stone Disease-Polygenic Meets Monogenic,

Néphrologie & Thérapeutique. 2021; 17:88-94.

[7] Hornberger B, Bollner MR, Kidney Stones, Physician Assist Clin. 2018; 1; 3:37-54.

[8] Ratkalkar VN, Kleinman JG, Mechanisms of Stone Formation, Clin Rev Bone Miner Metab. 2011; 9:187-197.

[9] Alok S, Jain SK, Verma A, Kumar M, Sabharwal M, Pathophysiology of Kidney, Gallbladder and Urinary Stones Treatment with Herbal and Allopathic Medicine: A Review, Asian Pac J Trop Dis. 2013; 1:496-504.

[10] Engels C, Gänzle MG, Schieber A, Fractionation of Gallotannins from Mango (Mangifera Indica L.) Kernels by High-Speed Counter-Current Chromatography and Determination of Their Antibacterial Activity, J Agric Food Chem. 2010; 27; 58:775-780.

[11] García-Perdomo HA, Solarte PB, España PP, Pathophysiology Associated with Forming Urinary Stones, Urología Colombiana. 2016; 1; 25:118-125.

[12] Tsujihata M, Miyake O, Yoshimura K, Kakimoto KI, Takahara S, Okuyama A. Fibronectin as A Potent Inhibitor of Calcium Oxalate Urolithiasis, J Urol. 2000; 164:1718-1723.

[13] Aggarwal KP, Narula S, Kakkar M, Tandon C, Nephrolithiasis: Molecular Mechanism of Renal Stone Formation and the Critical Role Played by Modulators, Biomed Res Int. 2013: 2-14.

[14] Ryall RL, The Possible Roles of Inhibitors, Promoters, and Macromolecules in the Formation of Calcium Kidney Stones, Urinary tract stone disease. 2010:31-60.

[15] Moe OW, Kidney Stones: Pathophysiology and Medical Management, The lancet. 2006; 28; 367:333-44.

[16] Khan A, Prevalence, Pathophysiological Mechanisms and Factors Affecting Urolithiasis, Int Urol Nephrol. 2018; 50:799-806.

[17] Türk C, Petřík A, Sarica K, Seitz C, Skolarikos A, et al, EAU Guidelines on Interventional Treatment for Urolithiasis. Eur Urol. 2016; 69:475-482.

[18] Dawson CH, Tomson CR, Kidney Stone Disease: Pathophysiology, Investigation and Medical Treatment, Clinical Medicine. 2012; 12:467.

[19] Vijaya T, Kumar MS, Ramarao NV, Babu AN, Ramarao N, Urolithiasis and its Causes-Short Review, J Phytopharmacol. 2013; 2:1-6.

[20] Queau Y, Nutritional Management of Urolithiasis, Vet Clin North Am Small Anim Pract. 2019; 49:175-186.

[21] Frassetto L, Kohlstadt I, Treatment and Prevention of Kidney Stones: An Update, Am Fam Physician. 2011; 84:1234-1242.

[22] Jung H, Andonian S, Assimos D, Averch T, Geavlete P, et al., Urolithiasis: Evaluation, Dietary Factors, and Medical Management: An Update of the 2014 SIU-ICUD International Consultation on Stone Disease, World J Urol. 2017; 35:1331-1340.

[23] Alelign T, Petros B, Kidney Stone Disease: An Update on Current Concepts, Adv Urol. 2018.

[24] Aggarwal R, Srivastava A, Jain SK, Sud R, Singh R, Renal Stones: A Clinical Review, EMJ Urol. 2017; 5:98-103.

[25] Miller NL, Lingeman JE, Management of Kidney Stones, Bmj, 2007; 334:468-472.

[26] Tonolini M, Villa F, Ippolito S, Pagani A, Bianco R, Cross-sectional Imaging of Iatrogenic Complications After Extracorporeal and Endourological Treatment of Urolithiasis, Insights into imaging. 2014; 5:677-689.

[27] Healy KA, Ogan K, Nonsurgical Management of Urolithiasis: An Overview of Expulsive Therapy, J Endourol. 2005; 19:759-767.

[28] Kachrilas S, Papatsoris A, Bach C, Bourdoumis A, Zaman F, et al., The Current Role of Percutaneous Chemolysis in the Management of Urolithiasis: Review and Results, Urolithiasis. 2013; 41:323-326.

[29] Pattaras JG, Moore RG, Citrate in the Management of Urolithiasis, J Endourol. 1999; 13:687-692.

[30] Joy JM, Prathyusha S, Mohanalakshmi S, Kumar AP, Kumar CK, Potent Herbal Wealth with Litholytic Activity: A Review. IJIDD. 2012; 2:66-75.

[31] Bashan I, Bozlu M. The Possible Litholytic Effect of *Ononis Spinosa* L. on various Human Kidney Stones- An in vitro Experimental Evaluation, J Herb Med. 2020; 1:22:100345.

[32] Sairi NH, Muhammad N, Pauzi AN, Bakar MF, Talip BH, et al., The Evaluation of Antiurolithiathic Properties of *Ananas nanus*, *Aquilaria malaccensis, Curcuma xanthorrhiza*, *Pandanus atrocarpus* and *Garcinia mangostana*, Materials Today: Proceedings, 2019; 19:1145-1150.

[33] Zaki S, Jahan N, Kalim M, Islam G, In vitro Antilithiatic Activity of The Hydro-Alcoholic Extract of *Cinnamomum zeylanicum* Blume Bark on Calcium Oxalate Crystallization, J Integr Med. 2019; 17:273-281.

[34] Bawari S, Sah AN, Tewari D, Anticalcifying Effect of *Daucus carota* in Experimental Urolithiasis in Wistar

rats. J Ayurveda Integr Med. 2020; 11:308-315.

[35] Agawane SB, Gupta VS, Kulkarni MJ, Bhattacharya AK, Koratkar SS, et al., Patho-Physiological Evaluation of *Duranta erecta* for the Treatment of Urolithiasis, J Ayurveda Integr Med. 2019; 10:4-11.

[36] Kaleeswaran B, Ramadevi S, Murugesan R, Srigopalram S, Suman T, Balasubramanian T. Evaluation of Anti-Urolithiatic Potential of Ethyl Acetate Extract of *Pedalium murex* L. on Struvite Crystal (Kidney Stone), J Tradit Complement Med. 2019; 9:24-37.

[37] Bano H, Jahan N, Makbul SA, Kumar BN, Husain S, et al, Effect of *Piper cubeba* L. Fruit on Ethylene Glycol and Ammonium Chloride Induced Urolithiasis in Male Sprague Dawley Rats, Integr Med Res. 2018; 7:358-365.

[38] Mittal A, Tandon S, Singla SK, Tandon C, Modulation of Lithiatic Injury to Renal Epithelial Cells by Aqueous Extract of *Terminalia arjuna*, J Herb Med, 2018; 13:63-70.

[39] Yachi L, Bennis S, Aliat Z, Cheikh A, Idrissi MO, et al., In vitro Litholytic Activity of Some Medicinal Plants on Urinary Stones, Afr J Urol, 2018; 24:197-201.

[40] Dinnimath BM, Jalalpure SS, Patil UK. Antiurolithiatic Activity of Natural Constituents Isolated from *Aerva lanata*. J Ayurveda Integr Med, 2017; 8:226-232.

[41] Sethiya NK, Brahmbhat K, Chauhan B, Mishra SH. Antiurolithiatic Activity of *Ensetesuperbum* (Roxb.) *Cheesman* (wild banana) pseudostem on Ethylene Glycol Induced Urolithiasis in Rats, Indian J Tradit Knowl. 2017; 16:303-309.

[42] Das P, Kumar K, Nambiraj A, Rajan R, Awasthi R, et al., Potential Therapeutic Activity *of Phlogacanthusthyrsi formis* (Mabb) Flower Extract and Its Bio fabricated Silver Nanoparticles Against Chemically Induced Urolithiasis in Male Wistar Rats, Int J Biol Macromol. 2017; 103:621-629.

[43] Goyal PK, Verma SK, Sharma AK, Antilithiatic Potential of *Vernonia cinerea* Against Calcium Oxalate Calculi in Experimental Rats, J Phytopharmacol. 2017; 6:149-155.

[44] Sikarwar I, Dey YN, Wanjari MM, Sharma A, Gaidhani SN, et al., *Chenopodium album* Linn. Leaves Prevent Ethylene Glycol-Induced Urolithiasis in Rats, J Ethnopharmacol. 2017; 195:275-282.

[45] Onaran M, Orhan N, Farahvash A, Ekin HN, Kocabıyık M, et al.,

Successful Treatment of Sodium Oxalate Induced Urolithiasis with *Helichrysum Flowers*, J Ethnopharmacol. 2016; 186:322-328.

[46] Kumar BN, Wadud A, Jahan N, Sofi G, Bano H, et al., Antilithiatic Effect of *Peucedanumgrande* CB Clarke in Chemically Induced Urolithiasis in Rats. J Ethnopharmacol. 2016; 194:1122-1129.

[47] Bashir S, Gilani AH, Siddiqui AA, Pervez S, Khan SR, Sarfaraz NJ, Shah AJ, Berberis *vulgaris* Root Bark Extract Prevents Hyperoxaluria Induced Urolithiasis in Rats. Phytother Res. 2010; 24:1250-5.

[48] Prajwala B, Raghu N, Gopinath TS, Shanmukhappa B, Karthikeyan M, Ashok G, et al. Berberine and Its Pharmacology Potential: A Review, European J Biomed Pharm. 2020; 7:115-123.

[49] Birdsall TC, Berberine: Therapeutic Potential of Alkaloid Found in Several Medicinal Plants. Altern Med Rev 1997; 2:94-103.

[50] Bousta D, Grafov A, Houssaini TS, Phytomolecules Investigated for The Prevention and Treatment of Urinary Stones. Mediterr J Chem. 2021; 11:126-132.

[51] Kachrilas S, Papatsoris A, Bach C, Bourdoumis A, Zaman F, et al., The Current Role of Percutaneous Chemolysis in the Management of Urolithiasis: Review and Results. Urolithiasis. 2013; 41:323-326.

[52] Pattaras JG, Moore RG, Citrate in the Management of Urolithiasis, J Endourol. 1999; 13:687-692.

[53] Joy JM, Prathyusha S, Mohanalakshmi S, Kumar AP, Kumar CK. Potent Herbal Wealth with Litholytic Activity: A Review. IJIDD. 2012; 2:66-75.

[54] Fukushima EO, Seki H, Ohyama K, Ono E, Umemoto N, Mizutani M, Saito K, Muranaka T, CYP716A Subfamily Members Are Multifunctional Oxidases in Triterpenoid Biosynthesis, Plant Cell Physiol. 2011; 52:2050-2061.

[55] Nagal A, Singla RK, Herbal Resources with Antiurolithiatic Effects: A Review. Indo Glob J Pharm Sci. 2013; 3:6-14.

[56] Anand R, Patnaik GK, Kulshreshtha DK, Dhawan BN, Antiurolithiatic Activity of Lupeol, The Active Constituent Isolated from *Crateva nurvala*, Phytother Res. 1994; 8:417-421.

[57] Abo-El-Sooud K, Hashem MM, Eleiwa MM, Gab-Allaha AQ, Antiurolithiatic Activity of Edible Plants and Products, Natural Product: An Indian Journal. 2012; 8:168-174.

[58] Lobine D, Ahmed S, Aschner M, Khan H, Mirzaei H, Mahomoodally MF. Antiurolithiatic Effects of Pentacyclic Triterpenes: The Distance Traveled from Therapeutic Aspects. Drug Dev Res. 2020; 81:671-684.

[59] Devkar RA, Chaudhary S, Adepu S, Xavier SK, Chandrashekar KS, Setty MM, Evaluation of Antiurolithiatic and Antioxidant Potential of Lepidagathis Prostrata: A Pashanbhed Plant, Pharm Biol. 2016; 54:1237-1245.

[60] Lee HJ, Jeong SJ, Park MN, Linnes M, Han HJ, Kim JH, Lieske JC, Kim SH, Gallotannin Suppresses Calcium Oxalate Crystal Binding and Oxalate-Induced Oxidative Stress in Renal Epithelial Cells, Biol Pharm Bull. 2012; 35:539-544.

[61] Izui S, Sekine S, Maeda K, Kuboniwa M, Takada A, Amano A, Nagata H, Antibacterial Activity of Curcumin Against Periodontopathic Bacteria, J Periodontol. 2016; 87:83-90.

[62] Rahman MU, Khan J, Jeyabalan G, Parveen G, Antiurolithiatic Activity of Curcumin Against Ethylene Glycol-Induced Urolithiasis in Male Wistar Rats, Int J Adv Pharm Med Bioallied Sci. 2018; 6:104-110.

[63] Zhai W, Zheng J, Yao X, Peng B, Liu M, Huang J, Wang G, Xu Y, Catechin Prevents the Calcium Oxalate Monohydrate Induced Renal Calcium Crystallization in NRK-52E Cells and The Ethylene Glycol Induced Renal Stone Formation in Rat, BMC Complement Altern. 2013; 13:1-1.