A Review on Clinical Complications and Effectiveness of Herbal Medication in Urolithiasis

Kishore Bandarapalle*[1], K. K. Rajasekhar[2], Kodadhavadi Mohammad Ishaqulla[3], Avvaru Sree Harsha[4], Mopuru Hemanth Yadav[5]

[1*]*Department of Pharmaceutics, Sri Padmavathi School of Pharmacy, Tiruchanoor, Tirupati, 517503.*

[2]*Department of Pharmaceutical Analysis, Sri Padmavathi School of Pharmacy, Tiruchanoor, Tirupati, 517503.*

[3]*Department of Pharmacy Practice, Sri Padmavathi School of Pharmacy, Tiruchanoor, Tirupati, 517503.*

[4]*Department of Pharmacy Practice, Sri Padmavathi School of Pharmacy, Tiruchanoor, Tirupati, 517503.*

[5]*Department of Pharmacy Practice, Sri Padmavathi School of Pharmacy, Tiruchanoor, Tirupati, 517503.*

[1]*kishore.brr89@gmail.com*, [2]*komarla.research@gmail.com*,
[3]*k.ishaq2001@gmail.com*,[4]*avvarusreeharsha@gmail.com*,
[5]*mopuruhemanth2001@gmail.com*

Corresponding Author
Name: Dr. Kishore Bandarapalle
Email: kishore.brr89@gmail.com

Abstract

Urolithiasis is one of the third most common disease of calculi formation in any part of urinary tract includes kidney, ureter and urinary bladder. Urolithiasis is a multifactorial disease; therefore, this review compiles the factors responsible in emergence of different types of calculi and the pathophysiology of calculi formation. The medical management of urolithiasis has witnessed a great change with wide range of treatment options comprises of medical expulsion therapy, surgical techniques, synthetic drugs and herbal medication. The options include medical expulsion therapy, surgical techniques and synthetic drugs treatment results lack of success rate, increase in rate of retreatment, recurrence and results in several complications. In present scenario the handling of urolithiasis is not only restricted with stone removal but also protect against from its complications and recurrence. Therefore now a day's herbal medication is attracting the attention due to its merits in curing the urolithiasis condition by minimizing all the draw backs accompanied with other treatment possibilities. A final outlook explains the eminence and effectiveness of herbal medication and beneficial to upcoming researchers to shift their attentiveness to traditional medicine in order to cure or prevent urolithiasis effectively.

Keywords : Urolithiasis, Calculi, Recurrence, Complications and Herbal medication.

1. Introduction:

Urolithiasis, the third customary disorders of the kidney system. It is a multifarious disease characterised by the development of calculi in any region of the urinary system, including the kidneys, ureters, bladder, and urethra [1]. The increased prevalence of renal calculi elevated the economic burden in both developing and developed countries. The increased prevalence of renal calculi elevated the economic burden in both developing and developed countries. Males are often more affected than females, especially between the ages of 20 and 50 years, with a recurrence incidence of 70-80% in males and 40-50% in females [2][3]. Urolithiasis is originated from the Greek words 'Auron' which means urine and 'Lithos' which means calculi. Calculi compilation entails multiple primary processes ranging from super saturation of urine , crystallisation of components, aggregation, and retention in urine [4]. Calculi are constructed of multiple components such as calcium, oxalate, uric acid, phosphate, cysteine, and so on. The majority of calculi, i.e., 80% of calculi, are calcium oxalate or in association with calcium phosphate, 15% are infection or struvite calculi, and 5-10% are uric acid calculi. Almost 90% of calculi are radiopaque, with some uric acid calculi being radiolucent. The pH of the urine has a significant influence on the different forms of calculi that develop. Alkaline urine stimulates the emergence of calcium phosphate and struvite calculi, whilst acidic urine results in uric acid, cysteine, and calcium oxalate calculi [5][6]. Significant variants in the chemical composition of calculi have been observed globally during the last decades, which may be attributed to variations in the environment, nutrition, and lifestyle. Struvite calculi, for example, are typically composed of magnesium aluminium phosphate; however this kind of calculi is scarcely encountered due to effective treatment of urinary tract infections. The most significant drawback of urinary calculi is their recurrence after treatment. The probability of recurrence was evidenced to be 40% after 5 years and 75% after 20 years. The most significant drawback of urinary calculi is their recurrence after treatment. The probability of recurrence was evidenced to be 40% after 5 years and 75% after 20 years.

2. Demographic data

Urolithiasis prevalence varies substantially by region and is strongly influenced by geographical area, racial distribution, socioeconomic status, and dietary habits. It accounts for up to 0.5-1.9 % in developed nations [7]. It happens more prevalently in hot, desert areas in temperate zones such as the Mediterranean, Scandinavia, Central Europe, the British Islands, Northern Australia, Northern India, and Pakistan [8]. Urinary calculi impact 15% of the population in North India, with 50% resulting in kidney loss or renal impairment. Few instances have been reported in Southern India as a result of Tamarind use on a regular basis. Urolithiasis originates between the ages of 20 to 49 years in 70-80% of males and 47-60% of females, with a 12% recurrence prevalence after 10 years [9]. Disease has a 10% lifetime prevalence in males and a 5% in women. Although females are less impacted than males, females manifest to be greater susceptible than before. It is present in both developing and developed nations as a result of socioeconomic variables and lifestyle changes [10]. From

1994 to 2011, the incidence of urolithiasis climbed from 1 in 20 to 1 in 11. It affects fewer children with a more risk in girls than boys and has an unknown aetiology.

In 2011, Australia had a substantial decline in struvite calculi, but other calculi remained the same, at 64%. Similarly, in Japan and India, the prevalence of calcium oxalate calculi is higher i.e.,92%, as is the incidence of struvite calculi i.e., 5.1% in females. It has grown exponentially in Spain from 4.2% in 1986 to 5% in 2011. Germany had 84% calcium oxalate calculi by 2006.

In the United States, more than 70% of calculi are calcium oxalate/phosphate, with uric acid accounting for 8-14% and struvite accounting for 2%. According to statistical estimates, the prevalence of calculi in paediatrics increased progressively in the United States, from 1 in 76000 in the 1950s to 1 in 1000 in the 1990s and 1 in 685 between 2002 and 2007. The male to female ratio in renal calculi is 4:1, and 30% to 40% of individuals had subsequent calculi following initial occurrence [11][12].

Urolithiasis incidence in Iran has climbed from 138 per 100,000 patients in 2005 to 241 per 100,000 patients in 2007, with the predominance of calculi having a mixed composition. Saudi Arabia has the highest lifetime risk of Urolithiasis, with a prevalence frequency of 20%. In China, it ranged from 1.5% in 1989 to 4% in 2000, whereas in Tunisia and Taiwan, it ranged from 50 to 83.7% [13].
Recurrence is a major issue with urolithiasis, with 50% of patients reporting recurrence within 5 years, rendering it a disease for life.

3. Types of renal calculi

Calcium calculi

Various factors responsible in formation of calcium calculi

- **Distal renal tubular acidosis**

One of the foremost crucial roles of the kidney is to regulate the body's acid-base balance. When acid levels in the systemic circulation build, the excess acid is discharged by the kidney via urine. If the renal tubules are incapable to eliminate excess acid from the systemic circulation, the disease is known as renal tubular acidosis. The body mobilises calcium and buffers such as phosphate and bicarbonate to buffer the excess acid in systemic circulation. It triggers a rise in the levels of calcium, phosphate, and bicarbonate in urine, which causes an elevation in the pH of the urine and facilitates the development of calcium phosphate calculi [14].

- **Primary hyperthyroidism**

To accomplish vital functions such as nerve impulse transmission, muscle contraction, blood coagulation, hormone production, and intracellular adhesion, the parathyroid glands produce the parathyroid hormone.

Primary hyperparathyroidism develops when one or more parathyroid glands become hyperactive, resulting in excessive parathyroid hormone production (PTH). The increased output of parathyroid hormone induces more calcium in the blood and urine, resulting bone thinning and calcium calculi in the kidney [15].

- **Hypocitraturia**

It emerges as a result of a reduction in citrate levels in urine, which forms a complex with calcium to produce a freely soluble complex known as calcium citrate. In the absence of citrate, calcium forms complexes with phosphate and oxalate, yielding calcium phosphate and calcium oxalate, both of which are extremely insoluble in nature [16][17].

- **Hyperoxaluria**

One of the predominant causes of calcium-based calculi is hyperoxaluria. Calcium oxalate calculi constitute for 70-80% among all calculi.

Reasons for hyperoxaluria condition are

- Increased intake of oxalate rich diet such as spinach, rhubarb, beets, cabbage, tomatoes, nuts, wheat bran, strawberries, tea etc.
- Gastro intestinal issues such as crohns disease (bowel disease) associated with trans mural inflammation in ileum. Ileum is responsible in reabsorption of fats and proteins. Due to crohns disease the ileum fails in absorption of fats. Usually calcium binds with oxalate in intestine and excreted through stools. Therefore if any oxalate rich diet was taken it excretes through stools by binding with calcium. Where as in crohns disease the undigested fats binds to calcium by preventing oxalate, the free oxalate gets absorbed from the gut results in increase in concentration of oxalate in blood (Hyperoxalmia) and urine (Hyperoxaluria) [18][19][20][21].
- Autosomal recessive disease

The enzymes such as alanine glyoxalate aminotransferase and D- glyceric dehydrogenase are involved in the metabolism of oxalate results in decrease concentration of oxalate in urine.

In autosomal recessive disease, a deficiency of alanine glyoxalate amino transferase and D-glyceric dehydrogenase, which are responsible for oxalate metabolism, resulting in increased oxalate concentration in urine, which leads to the production of calcium oxalate [22][23].

- **Idiopathic hypercalciuria**

The conditions responsible in increase the calcium concentration in urine are [24]

Dents disease

It is a proximal renal tubular disorder characterized by hypercalciuria, nephrocalcinosis, nephrolithiasis and may progress to renal failure [25].

Vitamin D

Vitamin D mainly its active metabolite calcitrol increases the digestive calcium absorption which reflects on increase calcium levels in urine provide wide chances for calcium calculi formation [26].

Polymorphism of calcium sensing receptor

The primary purpose of the calcium detecting receptor is to maintain calcium levels in the systemic circulation consistent so that the receptor may accomplish its essential functions. The polymorphism of the calcium detecting receptor causes hypercalciuria and is responsible for the production of calcium calculi [27].

Hyperuricosuria

This condition originates as a result of an excessive intake of purine-rich foods such as meat and fish, which causes an increase in uric acid production. The increasing concentration of uric acid contributes significantly to the formation of calcium calculi, especially calcium oxalate [28][29].

Uric acid calculi

Acidic urine

Acidic urine is majorly responsible in formation of uric acid calculi rather than hyperuricosuria i,e increase in concentration of uric acid in urine [30][31].
Uric acid solubility dropped from 750mg per litre in alkaline pH to 100 mg per litre in acidic pH. When protons react with uric acid at an acidic pH, protonated uric acid is formed. Uric acid calculi develop when the concentration of protonated uric acid exceeds 100 mg per litre and precipitates. At contrast, uric acid crystallises in alkaline pH if the uric acid concentration surpasses 750mg per litre. As a result, acidic urine is the most critical factor in the production of uric acid calculi in hyperuricosuria [32].

Hyperuricosuria

Hyperuricosuria means the increased excretion of uric acid in urine. The major reasons for increased excretion of uric acid in urine are

- **Excess intake of protein diet:** such as organ meet, red meet, pork, beer (alcoholic drink), sea foods (such as scallops, anchovies, cardines etc.) [33].
- **Myeloproliferative syndrome:** (excess production of RBCs and WBCs underwent excess purine metabolism during destruction of cells)
  Myeloproliferative disorder is accompanied by an overproduction of red and white blood cells. It induces a high turnover of blood cells, which implies that many cells are created and then destroyed. Because of the increased destruction of cells by damaging the nucleus, there is an increase in purine metabolism, which leads to an upsurge in uric acid synthesis, which increases blood circulation. Uric acid calculi are caused by an increase in uric acid [34].

- **Lesch – Nyhan syndrome:** (lack of hypoxanthine guanine phosphoribosyl transferase enzyme results in uric acid production)
  Lesch - Nyhan syndrome is a neurological disorder caused by a deficiency of the enzyme Hypoxanthine - Guanine Phosphoribosyl Transferase (HGPT). This enzyme is engaged in the purine salvage pathway. Purine bases are reutilized and converted into purine nucleotides via this mechanism. Hypoxanthine and guanine are transformed by the HGPRT enzyme into iosine monophosphate and guano sine monophosphate. During this process, phosphoribosyl pyrophosphate (PRPP) is involved, providing ribose phosphate and yielding inorganic pyrophosphate (PPI). Because the hypoxanthine - Guanine Phosphoribosyl Transferase enzyme (HGPRT) is completely absent, the levels of hypoxanthine, guanine, and phosphoribosyl pyrophosphate (PRPP) are elevated. By purine degradation pathway the elevated levels of hypoxanthine and guanine are converted into uric acid, which results in increased concentration of uric acid in urine may results in formation of uric acid calculi [35].

- **Gout:** (Too much uric acid crystals deposits in joints it occurs mainly due to Myeloproliferative syndrome)

- **Type II diabetis:** Patients with type II diabetes are more prone to uric acid calculi because their urine is acidic. The acidification of urine is mediated by an increase in net acid excretion (NAE) and a decline in the quantity of ammonium ion, both of which help to maintain the acid-base balance.Insulin resistance is the reason for reduced ammonia excretion as well as net acid excretion in type II diabetics. Insulin is responsible for stimulating ammonia production and sodium hydrogen exchange in the renal proximal tubule, which mediates ammonia excretion [36].

Struvite calculi

Struvite calculi are most frequently caused by urinary tract infections. The bacterial species that yields urease enzyme converts urea to ammonia and carbon dioxide. The synthesis of ammonia in urine raises the pH of the urine, turning it alkaline in nature. The alkaline pH of urine precipitates phosphates and magnesium, resulting in the production of magnesium ammonium phosphate [37][38].

Cystine calculi

Cysteine calculi typically arise as a result of a genetic disease in which the renal tubules fail to reabsorb cysteine amino acid from urine, resulting in increased cysteine excretion in urine. Excretion of cysteine without reabsorption from renal tubules is also not a problem because the cystine is soluble in urine upto 250 to 300 mg per liter in normal pH (i.e.. 6.2 – 6.8). If cystine concentration in urine is increases beyond the solubility limit leads crystallization and results in calculi formation [39][40][41].

4. Diet in relation to renal calculi:

Calcium is crucial in the production of urinary calculi. Oxalate absorption from the gut is inversely proportional to calcium dietary intake, i.e. less calcium intake leads to increased oxalate absorption from the intestine, resulting in enhanced concentration in urine. Calcium consumption of more than 1200 mg per day aids in the reduction of oxalate concentrations in urine and the inhibition of calcium oxalate calculi development. If the calcium intake is 800 mg per day, it is responsible for calcium imbalance and bone calcium loss [42][43].

A high-sodium diet is to responsible for an increase in urine calcium levels. Hypercalciuria is caused by elevated calcium levels, which results in the production of calcium-based calculi. Because of the concentration gradient created by sodium's active reabsorption, calcium is passively reabsorbed into the proximal tubule. A low sodium diet of 1800 - 2300 mg per day increases proximal sodium and passive calcium absorption by minimizing calcium loss into urine. Instead of limiting calcium intake, individuals with calcium-based calculi such as calcium oxalate and calcium phosphate calculi should consume less sodium. Now a days focus is shifted in limiting the sodium intake by pairing the calcium rich and oxalate rich foods is effective. Current guidelines recommend not more than 2300 mg of daily sodium intake.

Diet including red meat, poultry, egg, sea foods etc. rich in purine content. It increases the production of uric acid and get accumulate as crystals in the joints or in kidney as calculi. The increased uric acid levels show its impact on reducing the urinary citrate levels responsible in inhibition of calculi formation. This condition can be overcome by decrease intake of low animal protein diet and increase the healthy diet include the vegetables, fruits, whole grain and low fat dairy products decrease the urine acidity and it helps in reducing the chance of calculi formation [44].

Calcium oxalate calculi are the leading type in renal calculi. The oxalate levels are rich in many foods including vegetables and fruits. Vegetables rich in oxalate are beet root, spinach, rhubarb, potatoes, nuts etc. Beverages such as tea, coffee and cocoa consist of high oxalate content. Oxalate levels in urine increase due to the deficiency of the oxalate degrading bacteria in gastrointestinal tract which results in prevention of absorption of oxalate from gut wall [46]. The 10 - 20% of oxalate in urine is from absorbed dietary oxalate whereas the

remaining oxalate is as a result of endogenous production from two major precursors glyoxalate and ascorbic acid. Out of which 35 – 50% of urinary oxalate is from ascorbic acid and 50 – 70 % from the glyoxalate. The people suffering from calcium oxalate calculi are instructed to have the above mentioned foods in less amounts or prevent completely. The condition arises if mean urinary oxalate excretion is > 45mg per day. Intake of high calcium diet decreases the absorption of oxalate. Therefore the individuals suffering from increased oxalate levels are instructed to have adequate calcium. Having oxalate rich and calcium rich foods during meals gets bind to the stomach and intestine before the processing of kidney [46].

The main reason responsible for renal calculi is supersaturation of ions, salts results in crystal formation followed by crystal growth and aggregation. It is advised to have more and more fluid intake which dilutes the urine concentration of crystal forming ions and salts [47]. Increased uptake of fluids of more than three liters of water per day also flush the crystals of size less than 5mm which are enough results in large calculi. The epidemiologic studies stated that the intake of water, fluids should be such that at least 2.5 L urine output can prevent the formation of calculi. Fluids include water, citrus drinks like lemonade and orange juice rich in citrate which is a urinary calculi inhibitor. The role citrate in urine is to prevent the formation of insoluble calcium oxalate and phosphate by resulting in the formation of calcium citrate which is freely soluble. Some studies states that uptake of high quantities of vitamin C enhances the calculi formation because it converts into oxalate
The recurrence of calculi is minimized by fewer intakes of sodium, animal protein, oxalate rich diet, normal or high intake of calcium and excess fluid consumption.

Risk factors associated with renal calculi formation:

Age and sex: Frequency of Calculi formation is widely noticed at the age of 20-50 years. Prevalence of calculi is high in males in comparison to females (13%, 7% respectively) [48].
Diet: Excess intake of animal protein, sodium and deficiency of calcium intake, citrate, fibre and alkali foods leads to calculi formation, having less fluid intake.
Family history: Renal calculi in family history increase the risk of calculi formation by two to three folds than an individual with negative family history.
Dehydration: Loss of fluid intake in the form of sweat results in supersaturation of urine followed by calculi formation.
Urine composition: Excessive excretion of calculi forming promoters and decreased excretion of calculi inhibitors causes calculi formation.
Metabolic disorders: Hypercalciuria, Hyperoxaluria, Hyperuricosuria, Hypocitraturia and history of gout.
Anatomic abnormalities: Medullary sponge kidney disorder patient’s results in high risk of renal calculi and incidence of recurrence, ureteropelvic junction stenosis and horse shoe kidney [49].
Inflammatory bowel diseases and gastric bypass surgery: It affects the absorption of calcium ions, increases the precipitation of calcium and other calculi forming substances.

Intestinal oxalate degrading bacteria: Urine oxalate levels increases with the absence of intestinal oxalate degrading bacteria [50].

Seasonal changes: Incidence of calculi is observed mainly in summer than in winter due to dehydration. The dehydration supersaturates the calculi forming ions in urine results in renal calculi.

Drugs: Indinavir (a protease inhibitor), sulfadiazine(sulfonamides), triameterene and metabolites, Phenazopyridine metabolites, oxypurinol (Allopurinol metabolite), Calcium ceftriaxonate, amoxicillin trihydrate, calcium + vitamin D supplements, acetazolamide, uricosuric drugs, aluminium hydroxide, corticosteroids, naftidrofuryl oxalate, glucocorticoids, theophylline etc.

5. Clinical manifestations:

- Calculi formation causes flank pain which causes discomfort below the ribs and above the ileum. The pain associated only the side where calculi formed and lasts for 20-60 min. The pain in the back accompanied with nausea and vomiting.
- The flank pain shifted to lower abdomen results in groin pain.
- Blood in urine was observed (haematuria).
- Cloudy and foul smelling of urine was noticed.
- Fever and chills due to urinary tract infections.

6. Pathophysiology:

Renal calculi formation is a biological process involves physicochemical changes and supersaturation of urine. Supersaturation results in precipitation of solutes in urine leads to nucleation. Supersaturation of urine is influenced by the calculi forming substances such as calcium, oxalate, phosphate, uric acid, cystine and low urinary volume. Both pH and specific concentrations of excess substances influence the formation of calculi. Renal calculi formation is due to the imbalance between the urinary calculi inhibitors and promoters.

Steps involved in the formation of renal calculi:

Crystal nucleation: It is the initial step which involves the formation of nucleus termed as nidus from the supersaturated urine in kidney. The free atoms, molecules and ions in supersaturated urine form microscopic clusters and get precipitated. The nucleation starts with decrease in urinary calculi inhibitors over promoters. Existing epithelial cells, red blood cells, urinary cast and other crystals acts as nucleating centres in process of nuclei formation termed as heterogeneous nucleation. The process of nucleation is rapidly takes place.

Crystal growth: crystal growth takes place by two mechanisms i.e. either by aggregation of preformed crystals or by secondary nucleation of crystal. The process of formation of nidus (nucleation) is rapidly takes place if inhibitors are less than promoters. In case of crystal growth i.e. the aggregation of crystals is slow and long process to obstruct the renal tubules.

The calculus formed in the urine has an intimate contact with the renal tubular epithelial cell membranes. Lipids of epithelial cell membranes are involved in the nucleation of crystals.

Calculi aggregation: The small hard masses of calculi in urine sticks together to form large calculi. The calculi retains with in the kidney.

Crystal cell interaction: It is termed as attachment of crystals to the renal tubular lining with the epithelial cells. Crystal cell interaction results in redistribution of phospholipid phosphatidyl serine in renal epithelial cell surface. It activates the cytosolic phospholipase enzyme which produces the byproducts archedonic acid, assorted lyso phospholipids and ceremide. These byproducts trigger many signalling path ways in the epithelial cell. By products such as archedonic acid and lyso phospholipid causes mitochondrial damage, changes in the gene expression by free radical generation i.e. reactive oxygen species (ROS). The byproduct ceremide cause the following cellular responses such as membrane damage, cellular injury, proliferation, cytotoxicity etc. The reactive oxygen species enhance the epithelial cell membrane damage by unmasking the crystal binding sites; crystals adhered to the epithelial cell act as the centres for the nucleation for new calculi. Calculi damage the renal epithelial cell by enters into the cell by endocytosis. Calculi move to the basolateral side and providing centre for calculi growth in renal interstitial. The injured renal tubular epithelial cell inverts its membrane which is anionic act as site crystal adherence. Injured renal tubular epithelial cells produce many membrane vesicles acts as nucleators (nuclear promoters) of calculi. Injured epithelial cells release renal prothrombin fragment-I and anionic proteins induce calculi aggregation. Deposition of calculi on madin-darby canine kidney epithelial cells than at proximal tubular epithelial cells because of the presence of hyaluronan binding molecule. Therefore by blocking the crystal binding molecules such as osteopontin, hyluronic acid, sialic acid and monocyte chemo attractant protein -I on the epithelial cells is one of the approaches in preventing the calculi formation.

6. Diagnosis:

Imaging techniques used for diagnosis of calculi are:

Computed tomography: It is used for imaging the calculi in kidney by passing the low dose radiation. It gives better quality of imaging with accurate measuring of calculi size and location. The detection accuracy in imaging depends on calculi size, intensity, noise level and signal to noise ratio. The detection accuracy increases with increase in calculi size, intensity and signal to noise ratio and decreases with increase in noise level. Therefore difficult to identify the calculi of 5 mm in size due to the noise in imaging, fortunately the calculi of that size cannot cause ureteral obstruction. It is easy to image the calculi in case of obese patient also. It offers >95% sensitivity and 98% specificity. The major drawback is the amount of ionizing radiation particular in case of frequent calculi formers, pregnant women and young patients and costly. This method is used for imaging of radio opaque calculi such as calcium based calculi but not in case of uric acid calculi which is radiolucent in nature [51].

Ultrasonography: Calculi are detected by passing the short pulses through transducer. These waves propagate through the tissues and reflect back to the source. The probe used for detecting calculi is usually 3.5-5MHz. This technique is effective when patient is sensitive to

invasive radiation such as pregnant women and young patients, operator dependency and economical compare with non-contrast computer aided tomography scan. Though it has the merits over the non-contrast computer aided tomography scan the usage is limited due to its low sensitivity (45%) and specificity (88-94%) and in accurate measurement of calculi size. Sensitivity increases with increase in size of calculi. The sensitivity was found to be 13% for calculi less than 3 mm and increase to 71% in case of calculi more than 7mm. Ultrasonography usually overestimates the calculi size by 1.8 mm on average. This method used for imaging of both radio opaque and radiolucent calculi [52][53][54]

Plain X-rays: It helps in detecting of different types of calculi such as calcium oxalate, calcium phosphate, struvite and cystine calculi. It offers low radiation than CT scan (0.6 – 1 msv) and inexpensive, whereas sensitivity reported is low i.e. ranges between 29%-54%. With low sensitivity. Major drawback besides sensitivity is overlook of calculi located on the bone.

Intravenous pyelogram: It is a X-ray examination of kidney, ureter and urinary bladder by injecting the iodinated contrast material into veins. This method is replaced with CT scan. CT scan can do in faster manner as IVP often requires delayed imaging to allow contrast excretion into a partially obstructed collecting system.

7. Treatment options

Various treatment strategies are employed to treat urinary calculi condition based on the calculi size, location, degree of obstruction and kidney function.
Different approaches made in the treatment of renal calculi are

- Medical expulsion therapy
- Surgical techniques
- Synthetic drugs
- Herbal medication

Medical expulsion therapy: Medical expulsion therapy is employed if the size of calculi is <12mm. It promotes the spontaneous removal of calculi with medication such as alpha-1 adrenergic blockers, calcium blockers, phosphodiesterase-5 (PDE5) inhibitors and anti-inflammatory agents. It expels calculi by decrease uterine smooth muscle contraction and, there by expulsion of calculi from distal portion. Success rates are high with smaller the diameter of calculi [55][56].
Tamsulonin is frequently used α -D Adrenoceptor blockers in expelling the ureteral calculi from distal portion [57][58].
Success rate is based on size and location of calculi. A calculi of 1mm has 87% of chances of passage, 2-4mm of 76%, 5-7mm has 60%, 8-9mm has 48% and 10mm or large has 25% chances for passage. Similarly a proximal calculus has 48%, mid ureteral calculi has 60% and distal calculi has 75 to 79% chances of spontaneous passage. It has been predicted that the passage time for calculi for less than 2 mm is 8 days, 4-6 mm; it may take 22 days for the

passage of stones. Moreover this method is continued for more than 45 days which may leads to more complications.

Surgical techniques:

Surgical techniques are one of the effective methods of treatment in urolithiasis. It was reported as treatment option for calculi in Hindu and Greek writings. An ancient Indian surgeon named Sushruta (600 B.C) provided detailed description of 300 surgical procedures including perineal lithotomy. Hippocrates (460 to 370 B.C) reported that calculi surgery is a specialist skill. Ammonius (276 B.C) reported that crushing of bladder calculi makes easy removal of calculi. Method of calculi removal such as Litholopaxy introduced by Bigelow in 1874 and Cystotopic lithorite by Young and Mckay (1870-1945). A change made in method leads to extracorporeal shock wave lithotripsy was introduced at 1980's.

Extracorporeal Shockwave lithotripsy (ESWL):

This method involves fracture or disintegration of calculi by using focused shock waves. It is utilized to disintegrate the calculi size upto 1 cm effectively and it does not have high success rate if calculi size is ranging from 1 to 2 cm or more than 2 cm. The major drawback associated is whether the calculi is disintegrated to required size to pass through ureter is not clear, therefore rate of retreatment is increased. Limitations in usage include pregnancy condition, skin to calculi distance in obese patients and urinary tract infections. The placement of ureteral stunt with no usage of instrumentation is the advantage [60]. It is contraindicated in patients with anti - coagulant therapy and patients with UTI. Complications include bleeding, blood in urine and injury to GIT organs, long term effects of hypertension, renal function, bruising, nausea and vomiting. It is proved to be effective in treatment of renal calculi in paediatrics [61][62][63].

Uteroscopic Lithotripsy (URSL): In these method calculi is fragmented by using as energy via laser fibre through the scope. It is preferred widely in case of calculi size is upto 2 cm and in case of multiple calculi. This technique is performed by passing the uteroscope through the ureter which visualize the exact location of calculi as well as it is clear whether calculi disintegrates into required size to pass through ureter which is drawback in case of ESWL. High stone free rate and low retreatment rate is advantage with this technique in comparison with ESWL. The drawback include it demands more aesthesia, specialized trained person, stent placement, hospitalization and time consuming process compare with ESWL. The stunt is placed for a week after the uteroscopy procedure. In most of the patients the stunt may cause irritation in ureter and bladder results in complications such as cramping, discomfort and back pain during urination, blood in urine, frequent urination, urinary urgency and bladder pain [64].

By comparing the extracorporeal shockwave lithotripsy (ESWL) and uteroscopic lithotripsy (URSL), it is concluded that URSL is effective in case of stone free rate and the retreatment

rate compared to ESWL. If compared with operation time URSL need longer time than ESWL due to its high invasiveness [65][66].

Percutaneous nephrolithotomy (PCNL): It is a surgical procedure where surgeon makes a small incision about the size of a dyne in back and inserts a tube into kidney which breaks the stone into pieces. It is primary treatment option to clear the calculi of size >2cm. It is widely used in treatment of large and complex calculi with superior stone free rates in comparison to ESWL and URSL still with serious complications include haemoglobin drop, blood transfusion, damage of renal parenchyma and post-operative analgesic if the surgeon is less experienced. The complications increase with increase in calculi size. It pocess 100% stone free rate subject to calculi size less than 1 cm which was not revealed with ESWL and URSL. However it reduces the mortality and morbidity and remains the first line treatment of renal calculi. It requires a stunt and removes after a week of surgery. It may cause irritation in ureter and bladder results in complications such as cramping, discomfort and back pain during urination, blood in urine, frequent urination, urinary urgency, bladder pain. Usually ESWL is preferred for paediatrics in calculi treatment but now a days mini and micro PCNL is using for paediatrics with increased stone free rates [67][68].

Open or Laparoscopic surgery: It includes anatrophic nephrolithotomy and pyelolithotomy but are rarely used because it results in high morbidity and complication rates. Therefore these are generally reserved for selected cases. This technique is preferred in rare cases if ESWL, URSL and PCNL fail to treat calculi.

However these techniques are effective in treating calculi condition, but not resulted end point in calculi therapy, because the patients have a high incidence of recurrence of calculi and results in invasive complications such as haemorrhage, hypertension, tubular necrosis, fibrosis of kidney etc. and expensive.

After the surgical procedure the physician gives a strainer and collection bottle to patient to urinate and collect the stone pieces which may look like sand and gravel to analyse the type of calculi. Type of calculi is determined by urine analysis which helps to take specific measures including the medication and diet control to prevent the reoccurrence of calculi.

Synthetic drugs: Based on calculi type respective drugs are used in urinary calculi treatment.

Calcium oxalate and calcium phosphate:

Drugs employed in the treatment of calcium oxalate and calcium phosphate calculi are

- Thiazides such as chlorthaiazide, bendroflumethiazide, trichlormethiazide, hydrochlorothiazide, indapamide used to treat calcium related calculi by decrease in urine calcium levels by increase reabsorption of calcium from proximal renal tubule, thick ascending limb and distal convoluted tubule. It results in increase calcium in blood and increase the flux of calcium into bone [69][70][71].
- Citrate supplementation include potassium citrate, potassium magnesium citrate etc. It prevents the formation of calculi by forming complex with calcium which are freely soluble.

Combined administration of magnesium oxide and pyridoxine HCl results in decrease in calcium oxalate risk by effecting the absorption and synthesis of oxalate from gut wall and precursors respectively. Besides decrease in oxalate levels in urine it also increase the citrate concentration in urine by decline in reabsorption of citrate from renal tubule. It was reported that the magnesium supplementation should administer along with meals which enhance the solubility of magnesium salts and increase binding of magnesium with oxalate results in decreased urine oxalate levels [72][73].

Uric acid calculi:

- Treatment of uric acid calculi mainly involves urine alkalization to P^H ranges between 6.2-6.8 where the uric acid is soluble. Therefore potassium citrate or sodium bicarbonate is effective in urinary alkalization leads to solubilization of subsist calculi. The alkalization of urine should be within the limits i.e. not exceeds pH 6.5 which may causes the formation of calcium phosphate calculi. In such consequences potassium citrate is widely employed to alkalize the urine mean while prevents the calcium salt precipitation [74].
- Besides usage of urine alkalizing agents allopurinol is also extensively used to decrease the frequency of uric acid calculi by reducing the amount of uric acid made by the body. Allopurinol is xanthine oxidase inhibitor minimizes the production of uric acid by inhibiting the xanthine oxidase enzyme which plays a major role in converting purines into uric acid
- Excess intake of water prevents uric acid calculi by increase in urine volume which decreases the concentration of uric acid below to 100 mg per litre.

Struvite calculi:

These are known as triple phosphate or calcium magnesium aluminium phosphate and are formed due to urea splitting bacteria which hydrolyses the urea into ammonia there by increases the pH of the urine at which it is insoluble.

- By using anti microbials such as penicillin, ampicillin and tetracyclins which makes the urine sterile. It prevents the production of ammonia thereby increase in pH facilitates calculi formation due to the absence of urea splitting bacteria.
- Acetohydroxamic acid is employed to prevent struvite calculi by inhibiting the hydrolysis of urea into ammonia in urine infected with urea splitting bacteria results in decrease in ammonia levels there by decrease in pH 6. The calculi recurrence can be avoided even if patients with urinary infection not responding to specific antibiotic treatment. Its use is decreased due to its side effects including gastrointestinal upset, headaches, thrombophlebitis and rash [75].

Cystine calculi:

The cystine calculi solubility is enhanced by urinary volume and alkalization of urine above pH 7.

- Treatment involves urine alkalization to P^H more than 7 where the cystine is poorly soluble in normal urine pH ranges from 6.2 – 6.8. Therefore potassium citrate or sodium bicarbonate is

used in urinary alkalization leads to solubilization of cystine calculi by increase its solubility from 250 – 300 mg per litre at normal pH to 500 mg per litre at alkaline pH. Too much increase in pH of urine may also leads to precipitation of calcium phosphate calculi. Therefore care should be taken while increase in pH of the urine using suitable alkali such as potassium citrate which increase pH of urine and inhibit the calcium phosphate precipitation.

- A part from urinary alkalization cystine binding drugs sulfhydryl agents such as D-penicillamine or tiopronine and captopril are used. It forms highly soluble mixed disulphides with cystine moieties which prevents calculi formation. These drugs are associated with many side effects such as fever, rash, leukopenia, aplastic anaemia, proteinuria and hepatotoxicity [76].

Herbal medication:

The general problem the patient is experiencing with the surgical techniques and synthetic drug moieties are side effects during or after the therapy and the high incidence of recurrence of calculi. Therefore in order to minimize the side effects and recurrence of calculi the focus is shifted to herbal medication [77][78][79][80][81].

Medicinal plants played a major role in ancient traditional medicinal systems. Till today plants are one of the economical source of medicine for the majority of population with safe and minimal side effects. The world health organization also emphasized the utilization of herbal drugs and traditional medicine for the benefit of the world population due to cost effectiveness and less side effects [82][83][84][85]

Table 1: List of medicinal plants used in the treatment of urolithiasis.

Scientific name	**Part used**
Abelmoschus moschatus [86]	Seed
Acorus calamus [87]	Rhizome
Aerva lanata [88]	Areial parts
Asparagus racemosus [89]	Root
Berberis vulgaris [90] [91] [92]	Root
Boerhavia diffusa [93]	Root
Bombax ceiba [94]	Fruits
Benincasa hispida [95]	Seed
Biophytum sensitivum [96]	Whole plant
Bryophyllum pinnatum [97]	Leaf
Boldoa purpurscenes [98]	Leaf
Ceropegia bulbosa var. Lushii [99]	Root
Coleus Aromaticus Benth [100]	Leaves
Costus spiralis [101]	Whole plant
Cynodon dactylon [102]	Rhizome
Dolichos Biflorus [103]	Seed
Flos carthami [104]	Whole plant
Fucus vesiculosus [105]	Sea weed

Gokhsuradi Churan [106]	Ayurvedic Formulation (Mixture of plant extracts)
Helichrysum plicatum [107]	Flower
Hordeum vulgare [108]	Seed
Hygrophilia spinosa [109]	Whole plant
Ipomea eriocarpa [110]	Leaves
kalanchoe pinnata [111]	Leaves
Lantata camara [112]	Root
Leea macrophylla [113]	Whole plant
Lepidagathis prostrate [114]	Whole plant
Melia azedarach linn [115]	Leaves
Mimusops elangi [116]	Bark
Mitragyna parvifolia Korth. [117]	Root
Moringa olifera [118]	
Ocimum gratissimum [119]	Whole plant
Pergularia daemia [120]	Whole plant
Pinus maritime [121]	Seed
Punica granatum [122]	Fruits
Pinus eldarica [123]	Fruit
Raphanus sativas [124]	Bark
Rotula aquatica Lour [125]	Root
Sesbania grandiflora [126]	Leaves
Solanum xanthocarpum [127]	Fruit
Tribulus terrestris [128]	
Vernonia cinerea Less [129]	Whole plant
Urtica Dioica [130]	Leaves

8. Conclusion

urolithiasis is highly prevalent in present scenario and frequency of incidence is increasing compare to past in worldwide which effects the economic condition of the patient It arises due to supersaturation of calculi forming constituents due to changes in pH and more prevalent in men than in women. Many factors are responsible in formation of calculi such as metabolic, dietary, infection, environmental factors etc. Advanced technologies like computed tomography, ultrasonography, plain x-rays, IV pyelogram are used to diagnose the calculi formation. Based the size and location of calculi suitable treatment strategies are employed. Though medical expulsion therapy, Surgical techniques and synthetic drugs effective in treating the renal calculi condition due to complications, side effects and calculi reoccurrence the focus is shifted towards the herbal medication with minimal complications, side effects and decreased calculi recurrence. Several herbs are reported in having antiurolithiatic activity.

Acknowledgements

The first author wishes to express deepest gratitude to the Management and Prof. Dr. D. Ranganayakulu, M. Pharm., Ph.D., Principal, Sri padmavathi school of pharmacy, Tiruchanoor, Andhra Pradesh, India, for constant support.

REFERENCES

[1] Aggarwal A, Singla SK, Tandon C. Urolithiasis: Phytotherapy as an adjunct therapy. Indian J Exp Biol. 52(2) (2014) 103-111.

[2] Hosseinzadeh H, Khooei AR, Khashayarmanesh Z, Shariaty VM. Antiurolithiatic Activity of Pinus Eldarica Medw. Fruits Aqueous Extract in Rats. Urol J.2010;7(4): 232-37.

[3] Ghosh RB, Sur TK, Maity LN, Chakraborty SC. Antiurolithiatic activity of coleus Aromaticus Benth. In Rats. Anc Sci Life. 2000; 20(1-2): 44-47.

[4] Vyas N, Arga A. Antiurolithiatic Activity of Extract and Oleanolic Acid Isolated from the Roots of Lantana camara on Zinc Disc Implantation Induced Urolithiasis. ISRN Pharmacol. 2013; 1-5.

[5] Catherine C. Well, Kiran B. Chandrashekar, Garikiparthy N. Jyothirmayi, Vikesh Tahiliani, John C. Sabatino, Luis A. Juncos. Kidnay stones current diagnosis and management. Clinician reviews.2012; 22(2):31-37.

[6] Finlayson B. Physicochemical aspects of urolithiasis. Kidney Int.1978;13(5):344-360.

[7] Dharmalingam SR, Madhappan R, Chidambaram K, Ramamurthy S, Gopal K, Swetha P, Senthil Kumar KL. Anti-Urolithiatic Activity of Melia Azedarach Linn Leaf Extract in Ethylene Glycol-Induced Urolithiasis in Male Albino Rats. Trop J Pharm Res.2014; 13 (3): 391-397.

[8] Glina FP, Castro PMV, Monteiro GGR, Del Guerra GC, Glina S, Mazzurana M, Bernardo WM. The use of alpha-1 adrenergic blockers in children with distal ureterolithiasis. A systematic review and mata analysis. Int Braz J Urol. 2015; 41 (6): 1049-1057.

[9] Haiying zhang, ning li, kun li, peng li. Protective effect of Urtica dioica methanol extract against experimentally induced urinary calculi in rats. Mol Med Rep. 2014;10(6):3157-62.

[10] Robertson WG. Dietary recommendations and treatment of patients with recurrent idiopathic calcium stone disease. Urolithiasis.2016;4(1):9–26.

[11] Jianfei Liu, Shijun Wang, Evrim B. Turkbey. Computer-aided detection of renal calculi from noncontrast CT images using TV-flow and MSER features. Med. Phys.2015; 42 (1):144-153.

[12] Brikowski TH, Lotan Y, Pearle MS. Climate related increase in the prevalence of urolithiasis in the United States. *Proc Natl Acad Sci* .2008;105 (28):9841-9846.

[13] Sudabeh A, Pourmand G, Fatih El Howairis ME, Buchholz N, Najafi I, Reza Pourmand M, Mashhadi R, Pourmand N. National Profiles of Urinary Calculi A Comparison Between Developing and Developed Worlds. Iranian J Kidney Diseases. 2016;10(2):51-61.

[14] G.M. Preminger, K. Sakhaee, C. Skurla, C.Y. Pak, Prevention of recurrent calcium stone formation with potassium citrate therapy in patients with distal renal tubular acidosis, J Urol. 1985; 134(1):20-23.

[15] A.R. Lila, V. Sarathi, V. Jagtap, T. Bandgar, P. S. Menon, N. S. Shah, Renal manifestations of primary hyperparathyroidism, Indian J Endocrinol Metab. 16(2) (2012) 258–262.

[16] J.M. Zuckerman, D.G. Assimos, Hypocitraturia: Pathophysiology and Medical Management, Rev Urol. 11(3) (2009) 134–144.

[17] R. Caudarella, F. Vescini, Urinary citrate and renal stone disease: the preventive role of alkali citrate treatment, Arch Ital Urol Androl. 81(3) (2009) 182-7.
[18] Khan SR. Hyperoxaluria-induced oxidative stress and antioxidants for renal protection. Urol Res.2005;33(5):349-57.
[19] Rushton HG, Spector M. Effects of magnesium deficiency on intratubular calcium oxalate formation and crystalluria in hyperoxaluric rats. J Urol.1982; 127(3):598-604.
[20] Grases F, Bauzá AC, Prieto RM, Servera A. Internalization of Calcium Oxalate Calculi Developed in Narrow Cavities. Urol Case Rep 2014; 2(2): 51-53.
[21] Williams HE, Wandzilak TR. Oxalate synthesis, transport and the hyperoxaluric syndromes. J Urol.1989; 141(3):742-749.
[22] R. Hautmann, F.J. Hering, W. Lutzeyer, Calcium oxalate stone disease: effects and side effects of cellulose phosphate and succinate in long-term treatment of absorptive hypercalciuria or hyperoxaluria, J Urol. 120(6) (1978) 712-5.
[23] S. Joshi, W. Wang , S.R. Khan, Transcriptional study of hyperoxaluria and calcium oxalate nephrolithiasis in male rats: Inflammatory changes are mainly associated with crystal deposition, PLoS One. 12(11) (2017) 1-21.
[24] Robertson WG. Dietary recommendations and treatment of patients with recurrent idiopathic calcium stone disease. Urolithiasis.2016;4(1):9–26.
[25] O. Devuyst, R.V. Thakker, Dent's disease, Orphanet J Rare Dis. 5(28) (2010) 1-8.
[26] S. Tavasoli, M. Taheri M, Vitamin D and calcium kidney stones: a review and a proposal, Int Urol Nephrol. 51(1) (2019) 101-111.
[27] G. Vezzoli, A. Terranegra, T. Arcidiacono, R. Biasion, D. Coviello, M.L. Syren, V. Paloschi, S. Giannini, G. Mignogna, A. Rubinacci, A. Ferraretto, D. Cusi, G. Bianchi, L.

[28] P.K. Grover, R.L. Ryall, V.R. Marshall, Effect of urate on calcium oxalate crystallization in human urine: evidence for a promotory role of hyperuricosuria in urolithiasis, Clin Sci (Lond). 79(1) (1990) 9-15.
[29] O. Arowojolu, D.S. Goldfarb, Treatment of calcium nephrolithiasis in the patient with hyperuricosuria, J Nephrol. 27(6) (2014) 601–605.
[30] P. Ferrari, O. Bonny, Diagnosis and prevention of uric acid stones, Ther Umsch. 61(9) (2004) 571-4.
[31] Samal L, Pattanaik AK, Mishra C, Maharana BR, Sarangi LK, Baithalu RK. Nutritional stretegies to prevent Urolithiasis in Animals. Vet. World. 2011;4(3):142-144.
[32] M.R. Wiederkehr, O.W. Moe, Uric Acid Nephrolithiasis: A Systemic Metabolic Disorder, Clin Rev Bone Miner Metab. 9(3-4) (2011) 207–217.
[33] T.C. Ngo, D.G. Assimos, Uric Acid Nephrolithiasis: Recent Progress and Future Directions, Rev Urol. 9(1) (2007) 17–27.
[34] H.S. Mirheydar, P. Banapour, R. Massoudi, K.L. Palazzi, R. Jabaji, E.G. Reid, F.E. Millard, C.J. Kane, R.L. Sur, What is the incidence of kidney stones after chemotherapy in patients with lymphoproliferative or myeloproliferative disorders?, Int Braz J Urol. 40(6) (2014) 772-80.
[35] L. B. E. Shields, D.S. Peppas, E. Rosenberg, Xanthine calculi in a patient with Lesch-Nyhan syndrome and factor V Leiden treated with allopurinol: case report, BMC Pediatr. 18 (231) (2018) 1-5.

[36] C.Y. Pak, K. Sakhaee, O. Moe, G.M. Preminger, J.R. Poindexter, R.D. Peterson, P. Pietrow, W. Ekeruo, Biochemical profile of stone-forming patients with diabetes mellitus, Urology. 61(3) (2003) 523-7.

[37] R.K. Flannigan, A. Battison, S. De, M.R. Humphreys, M. Bader, E. Lellig, M. Monga, B.H. Chew, D. Lange, Evaluating factors that dictate struvite stone composition: A multi-institutional clinical experience from the EDGE Research Consortium, Can Urol Assoc J. 12(4) (2018) 131–136.

[38] Makhdoomi DM, Gazi MA. Obstructive urolithiasis in ruminants – A review. Vet. World, 2013; 6(4): 233-238.

[39] K. Ahmed, P. Dasgupta, M. Shamim Khan, Cystine calculi: challenging group of stones, Postgrad Med J. 82(974) (2006) 799–801.

[40] Carla GM, Dawn SM. Genetic Determinants of Urolithiasis.Nat Rev Nephrol. 2011;8(3):151-162.

[41] Cohen TD, Streem SB, Hall P. Clinical effect of captopril on the formation and growth of cystine calculi. J Urol. 1995 Jul;154(1):164-6.

[42] Sohgaura A, Bigoniya P. A review on epidemiology and etiology of renal stone. Am.J.Drug Discov.Dev. 2017; 7(2):54-62.

[43] Nishiura JL, Martini LA, Mendonça CO, Schor N, Heilberg IP. Effect of calcium intake on urinary oxalate excretion in calcium stone forming patients. Braz J Med Biol Res. 2002;35:669-75.

[44] Abba Y, Abdullah FF, Daud NH, Shaari RB, Tijjani A, Sadiq MA, Mohammed K, Adamu L, Mohd AM. Clinical management of dietary induced urolithiasis associated with balanoposthitis in a Boer goat. Open Vet J.2011; 5(1): 30-33.

[45] Allison M.J, Cook N.M. Oxalate degradation by gastrointestinal bacteria from humans. J. Nutr. 1986: 116; 455-460.

[46] Daudon M, Jungers P. Drug induced renal calculi: Epedemiology, prevention and management. Drugs. 2004; 64(3): 245-275.

[47] Erwin D, Roberts JA, Sledge G, Bennett Di, Finlayson B: Estimating urine supersaturation: A comparison of the result of two methods of evaluating changes induced by drinking milk, in Urolithiasis. Research.1976;261-264.

[48] Abdel-Halim RE. Urolithiasis in adults. Saudi Med J. 2005;26 (5):705-713.

[49] Raj GV, Auge BK, Assimos D, Preminger GM. Metabolic abnormalities associated with renal calculi in patients with horseshoe kidneys. J Endourol 2004;18:157‑61.

[50] Afkari R, Feizabadi MM, Ansari-Moghadam A, Safari T, Bokaeian M. Simultaneous use of oxalate-degrading bacteria and herbal extract to reduce the urinary oxalate in a rat model: A new strategy. Int Braz J Urol. 2019;45(6):1249-1259.

[51] Eiber M, Holzapfel K, Frimberger M, Straub M, Schneider H, Rummeny EJ, Dobritz M, Huber A. Targeted dual-energy single-source CT for characterisation of urinary calculi: experimental and clinical experience. Eur Radiol. 2012;22(1):251-8.

[52] Kanno T, Kubota M, Sakamoto H, Nishiyama R, Okada T, Higashi Y, Yamada H. The efficacy of ultrasonography for the detection of renal stone. *Urology*. 2014;84(2):285–288.

[53] Mojtaba Fazel, Mohammed IMGubari, Mahmoud Yousefifard, Mostafa Hosseini. Ultrasonography in Detection of Renal Calculi in Children; a Systematic Review and Meta-analysis. Arch Acad Emerg Med. 2019;7(1):1-11.

[54] Mohankumar Vijayakumar, Arvind Ganpule, Abhishek Singh, Ravindra Sabnis, Mahesh Desai. Review of techniques for ultrasonic determination of kidney stone size. Res Rep Urol. 2018;10: 57–61.

[55] Shafi H, Moazzami B, Pourghasem M. An overview of Treatment options for urinary stones. Caspian J Intern Med 2016; 7(1):1-6.

[56] Fink HV, Wilt TJ, MD, MPH; Eidman KE, Garimella PS, MacDonald R, Indulis R. Brasure M, Kane RL, Ouellette J, Monga M. Medical Management to Prevent Recurrent Nephrolithiasis in Adults: A Systematic Review for an American College of Physicians Clinical Guideline. Annals of Internal Medicine. 2013;158(7):535-43.

[57] Rong-zhen Tao, Zhi-qiang Qin, Fa-de Liu, Jian-lin Lv. Efficacy and Safety of Tamsulosin in the Medical Expulsion Therapy for Distal Ureteral Calculi. Urol J. 2019 Jun 17;16(3):224-231.

[58] Thijs Campschroer, Xiaoye Zhu, Robin WM Vernooij, MTW Tycho Lock. Alpha-blockers as medical expulsive therapy for ureteral stones. BJU Int. 2018;122(6):932-945.

[59] Dayel AA, Egail SA, Ezzibdeh MY, Oraifi IA, Sayed EE, Zallat AA. Treatment of ureteral stones: Extracorporeal shock wave lithotripsy versus ureteroscopy. Urol Ann.2015; 7 (3):182.

[60] Krishnappa C, bdul Wahab KS, Jha A, Roshdi S, Jacob T. Extra corporeal shock wave lithotripsy for vesical stone. Urol Ann.2015;7(3):182.

[61] Griffin SJ, Margaryan M, Archambaud F, Sergent-Alaoui A, Lottmann HB. Safety of shock wave lithotripsy for treatment of pediatric urolithiasis: 20-year experience. J Urol. 2010; 183(6): 2332-6.

[62] Yasser AN, Mohamed AE, Andoniana S. Changes in Urolithiasis Referral Patterns for Shock Wave Lithotripsy over a Decade: Was There Adherence to AUA/EAU Guidelines. Curr Urol.2015;8(3):144–148.

[63] Begun FP, Knoll CE, Gottlieb M, Lawson RK. Chronic effects of focused electrohydraulic shock waves on renal function and hypertension. J Urol.1991;145(3):635-639.

[64] Oliver R, Wells H, Traxer O, Knoll T, Aboumarzouk O, Biyani CS, Somani BK. Ureteric stents on extraction strings: a systematic review of literature. Urolithiasis.2016; 46(2):129-136

[65] Rukin NJ, Somani BK, Patterson J, Grey BR, Finch W, McClinton S, Parys B, Young G, Syed H, Myatt A, Samsudin A, John AI, Smith D. Tips and tricks of ureteroscopy: consensus statement. Part I. Basic ureteroscopy. Cent European J Urol.2015; 68:439-446.

[66] Alenezi H, Denstedt JD. Flexible ureteroscopy: Technological advancements, current indications and outcomes in the treatment of urolithiasis. Asian J Urol.2015;2(3): 133-141.

[67] Yunjin Bai, Yin Tang, Lan Deng, Xiaoming Wang, Yubo Yang, Jia Wang, Ping Han. Management of large renal stones: laparoscopic pyelolithotomy versus percutaneous nephrolithotomy. BMC Urology. 2017; 17:75.

[68] Sun H, Zhang Z, Yuan J, Liu Y, Lei M, Luo J, Shaw PW, Zeng G. Safety and efficacy of minimally invasive percutaneous nephrolithotomy in the treatment of patients with medullary sponge kidney. Urolithiasis, 2016; 44(5):421-6.

[69] Finlayson B Zisman AL. Effectiveness of treatment modalities on kidney stone recurrence. Clin J Am Soc Nephrol.2017; 12(10):1699-1708.

[70] BergslandKJ, WorcesterEM, Coe FL. Role of proximal tubule in the hypocalciuric response to thiazide of patients with idiopathic hypercalciuria. Am J Physiol Renal Physiol. 2013; 305(4):592–599.

[71] Nijenhuis T, Vallon V, van der Kemp AW, Loffing J, Hoenderop JG, Bindels RJ: Enhanced passive Ca21 reabsorption and reduced Mg21 channel abundance explains thiazide-induced hypocalciuria and hypomagnesemia. J Clin Invest. 2005;115(6):1651–1658.

[72] Rattan V, Sindhu H, Vaidyanathan S, Thind S K, Nath R. Effect of combined supplementation of magnesium oxide and pyridoxine in calcium-oxalate stone formers. Urol Res. 1994;22(3):161-5.

[73] Jill lindberg, Jean harvey, Charles y. c. pak. Effect of magnesium citrate and magnesium oxide on the crystallization of calcium salts in urine: changes produced by food-magnesium interaction. J Urol. 1990;143(2):248-51.

[74] Ferrari P, Bonny O. Diagnosis and prevention of uric acid stones. Ther Umsch. 2004 Sep;61(9):571-4.

[75] Martelli A, Buli P, Cortecchia V. Urease inhibitor therapy in infected renal stones. Eur Urol. 1981;7(5):291-3.

[76] Moore SL, Somani BK, Cook P. Journey of a cystinuric patient with a long-term follow-up from a medical stone clinic: necessity to be SaFER (stone and fragments entirely removed). Urolithiasis. 2019;47(2):165-170.

[77] Asilbek Gaybullaev, Saidakhror Kariev. phytotherapy of calcium urolithiasis with extracts of medicinal plants: changes of diuresis, urine ph and crystalluria. Med Health Sci J, 2012; 10: 74-80.

[78] Bathini Santhoshi, Vijay R C, Uma Maheshwara Rao V. A brief review on the potential medicinal plants and screening models of urolithiasis. Int J App Biol Pharm Tech. 2015; 6(1): 37-45.

[79] Grases, F., Prieto, R.M., Gomila, I., Sanchis, P., Costa-Bauza, A. Phytotherapy and renal stones: the role of antioxidants A pilot study in Wistar rats. Urol Res.2009; 37(1):35–40.

[80] Tsai CH, Chen YC, Chen LD, Pan TC, Ho CY, Lai MT, Tsai FJ, Chen WC. A traditional Chinese herbal antilithic formula, Wulingsan, effectively prevents the renal deposition of calcium oxalate crystal in ethylene glycol-fed rats. Urol Res.2008; 36(1): 17–24.

[81] Verma NK, Patel SS, Saleem TSM, Christina AJM, Chidambaranathan N. Modulatory effect of NONI-Herbal formulation against ethylene glycol-induced nephrolithiasis in albino rats. J Pharm Sci Res.2009; 3:83–89.

[82] Sudha Revathy S, Chitra Jeyaram, Murugesan M, Ramasamy. Invitro free radical scavenging activity of a siddha herbo mineral drug – kara sooda sathu parpam. Indo American J Pharm Res, 2014; 4(11): 5148-54.

[83] Butterweck V, Khan SR. Herbal Medicines in the Management of Urolithiasis: Alternative or Complementary? Planta Med. 2009; 75(10): 1095-103.

[84] Nirumand MC, Hajialyani M, Rahimi R, Farzaei MH, Zingue M, Nabavi SM, Bishayee A. Dietary Plants for the Prevention and Management of Kidney Stones: Preclinical and Clinical Evidence and Molecular Mechanisms. Int J Mol Sci. 2018;19(3):1-24.

[85] Santhoshi B, Chidrawar VR, Maheshwara Rao VU. Brief review on the potential medicinal plants and screening models of urolithiasis. Int J App Biol Pharm Tech. 2015;6(1):37-45.

[86] Anil T, Pawar, Niraj S. Vyawahare. Antiurolithiatic activity of Abelmoschus moschatus seed extracts against zinc disc implantation inducedurolithiasis in rats. J Basic Clin Pharm. 2016; 7(2):33-37.

[87] Hardik Ghelani, Maunik Chapala, Pinakin Jadav. Diuretic and antiurolithiatic activities of an ethanolic extract of Acorus calamus L. rhizome in experimental animal models. J Tradit Complement Med. 2016; 6(4):431-436.

[88] Soundararajan P, Mahesh R, Ramesh T, Begum VH. Effect of aerva lanata on calcium oxalate uroithiasis in rats. Ind J Exp biology.2006, 44(12) ; 981-86.

[89] Jagannath N, Asha P Dass, Khasif Ahmed. A study Antiurolithiatic Activity of ethanolic extract of *Asparagus racemosus* in animal models. Int J Pharm Res.2015; 5(11) :316-19.

[90] Samra Bashir, Anwar H. Gilani, Anwar A. Siddiqui, Shahid Pervez, Saeed R. Khan, Noor Jehan Sarfaraz, Abdul Jabbar Shah. *Berberis vulgaris* Root Bark Extract Prevents Hyperoxaluria Induced Urolithiasis in Rats. *Phytother. Res.* 2010; 24: 1250–1255.

[91] Vasavan Jyothilakshmi, Ganesan Thellamudhu, Alok Kumar, Anil Khurana, Debadatta Nayak, Periandavan Kalaiselvi. Preliminary investigation on ultra high diluted B. vulgaris in experimental urolithiasis. Homeopathy. 2013; 102: 172-178.

[92] Shirin Asgharian, Zahra Lorigooini, Reza Rafieian, Mahmoud Rafieian-Kopaei, Soleiman Kheiri, Hamid Nasri. The preventive effect of *Berberis vulgaris* extract on contrast-induced acute kidney injury. J Nephropathol. 2017;6(4):395-398.

[93] Balaji L G, Banji D, Banji JF. Evaluation of antiurolithiatic activity of the aqueous and alcoholic extracts of roots of boerhaavia diffusa. Indo American Journal of Pharm Research. 201;.5(1); 525-30.

[94] Gadge NB, Jalalpure SS. Curative treatment with extracts of Bombax ceiba fruit reduces risk of calcium oxalate urolithiasis in rats. Pharml Biol.2012;50(3): 310–317.

[95] Patel RK, Patel SB, Shah JG. Anti-Urolithiatic Activity of Ethanolic Extract of Seeds of *Benincasa Hispida.* Pharmacologyonline.2011;3:586-91.

[96] Pawar AT, Vyawahare NS. Anti-urolithiatic activity of standardized extract of *Biophytum sensitivum* against zinc disc implantation induced urolithiasis in rats. J Adv Pharm Technol Res.2015; 6(4):176-82.

[97] Yadav M, Gulkari VD, Wanjari MM. Bryophyllum pinnatum leaf extracts prevent formation of renal calculi in lithiatic rats. Ancient Sci Life. 2016;36:90-7.

[98] Dulce María González Mosqueraa, Yannarys Hernández Ortegaa, Pedro César Querob, Rafael Sosa Martínezb, Luc Pietersc. Antiurolithiatic activity of Boldoa purpurascens aqueous extract: An in vitro and in vivo study. J Ethnopharmacol. 2020; 21(253):1-9

[99] Monika J, Anil B, Aakanksha B, Priyanka P. Isolation, Characterization and Invitro Antiurolithiatic activity of Cerpegin Alkaloid from *ceropegia bulbosa* var. Lushii root. Int. J. Drug Dev. & Res.2012; 4(4):154-160.

[100] Ghosh RB, Sur TK, Maity LN, Chakraborty SC. Antiurolithiatic activity of coleus Aromaticus Benth. In Rats. Anc Sci Life. 2000; 20(1-2): 44-47.

[101] Araújo Viel T, Diogo Domingos C, da Silva Monteiro AP, Riggio Lima Landman MT, Lapa AJ, Souccar C. Evaluation of the antiurolithiatic activity of the extract of Costus spiralis Roscoe in rats. J Ethnopharmacol.1999; 66(2):193-8.

[102] Atmani, F., Sadki, C., Aziz, M., Mimouni, M., Hacht, B. Cynodon dactylon extract as a preventive and curative agent in experimentally induced nephrolithiasis. Urol Res.2009; 37(2):75–82.

[103] Atodariya U, Barad R, Upadhyay S, Upadhyay U. Anti-Urolithiatic Activity of *Dolichos Biflorus* Seeds. Journal of Pharmacognosy and Phytochemistry. 2013; 2(2):209.

[104] Lin WC, Lai MT, Chen HY, Ho CY, Man KM, Shen JL, Lee YJ, Tsai FJ, Chen YH, Chen WC. Protective effect of Flos carthami extract against ethylene glycol induced urolithiasis in rats. Urol Res.2012; 40(6):655-61.

[105] Veena C, Josephine A, Preetha S, Varalakshmi P. Beneficial role of sulfated polysaccharides from edible seaweed Fucus vesiculosus in experimental hyperoxaluria. Food Chemistry.2007;100 (4):1552-9

[106] A.K. Bagepalli Srinivasa, L. Kuruba, S. Khan, G.S. Saran, Antiurolithiatic Activity of Gokhsuradi Churan, an Ayurvedic Formulation By In Vitro Method, Adv Pharm Bull. 3(2) (2013) 477–479.

[107] Bayir Y, Halici Z, Keles MS, Colak S, Cakir A, Kaya Y, Akcay F. Helichrysum plicatum DC. subsp. plicatum extract as a preventive agent in experimentally induced urolithiasis model. J Ethnopharmaco.2011;138(2): 408– 414.

[108] Jignesh G. Shah, Bharat G. Patel, Sandip B. Patel, Ravindra K. Patel. Antiurolithiatic and antioxidant activity of Hordeum vulgare seeds on ethylene glycol-induced urolithiasis in rats. Ind J Pharmacol.2012;44(6): 672-77.

[109] Kundan G I, Thakurdesai PA, Vyawahare NS. Effect of Hygrophila spinosa in ethylene glycol induced nephrolithiasis in rats. Indian J Pharmacol.2012; 44(5): 639-42.

[110] Das M, Malipeddi H. Antiurolithiatic activity of ethanol leaf extract of Ipomoea eriocarpa against ethylene glycol induced urolithiasis in male Wistar rats. Indian J Pharmacol.2016; 48(3):270-4.

[111] Ramesh K, Paari E, Rajeshkumar S. In-vivo nephroprotective activity of kalanchoe pinnata leaves on ethylene glycol induced urolithiasis in albino rats. Indo American Journal of Pharm Research.2014; 4(7):3093-98.

[112] Vyas N, Arga A. Antiurolithiatic Activity of Extract and Oleanolic Acid Isolated from the Roots of *Lantana camara* on Zinc Disc Implantation Induced Urolithiasis. ISRN Pharmacol. 2013; 1-5.

[113] Nizami AN, Rahman MA, Ahmed NU, Islam MS. Whole Leea macrophylla ethanolic extract normalizes kidney deposits and recovers renal impairments in an ethylene glycol-induced urolithiasis model of rats. Asian Pac J Trop Med. 2012;5(7):533-8.

[114] Raviraj Anand Devkar, Shilpee Chaudhary, Sahithi Adepu, Seena Kanniparambil Xavier, Kodangala Subraya Chandrashekar, and Manganahalli Manjunath Setty. Evaluation of antiurolithiatic and antioxidant potential of Lepidagathis prostrata: A Pashanbhed plant. Pharm Biol. 2016;54(7):1237-45.

[115] Dharmalingam SR, Madhappan R, Chidambaram K, Ramamurthy S, Gopal K, Swetha P, Senthil Kumar KL. Anti-Urolithiatic Activity of Melia Azedarach Linn Leaf Extract in

Ethylene Glycol-Induced Urolithiasis in Male Albino Rats. Trop J Pharm Res.2014; 13 (3): 391-397.

[116] Purnima A, Basavaraj CK, Vishwanathswamy AHM. Antiurolithiatic and antioxidant activity of Mimusops elengi on ethylene glycol-induced urolithiasis in rats. Indian J Pharmacol. 2010;42(6):380-383.

[117] Ghosh R, Murali A, Ramu S. Diuretic effects of *Mitragyna parvifolia Korth.* root extract and its therapeutic efficacy against experimental urolithiasis in rats. Spatula DD. 2015;5(2):113-121.

[118] Karadi RV, Gadge N, Alagawadi KR, Savadi RV. Effect of *Moringa oleifera* Lam. root-wood on ethylene glycol induced urolithiasis in rats. J Ethnopharmacol.2006;105(1-2):306-11.

[119] Agarwal K, Varma R. *Ocimum gratissimum* L.: A Medicinal Plant with Promising Antiurolithiatic Activity. Int J Pharm Sci Drug Res. 2014; 6(1):78-81

[120] Vyas BA, Vyas RB, Joshi SV, Santani DD. Antiurolithiatic Activity of Whole-Plant Hydroalcoholic Extract of Pergularia daemia in Rats. J Young Pharm.2011;3(1):36-40.

[121] Busserolles J, Gueux E, Balasinska B. In vivo antioxidant activity of procyanidin-rich extracts from grape seed and pine (Pinus maritima) bark in rats. Int J Vitam Nutr Res.2006;76 (1):22-7.

[122] Rathoda NR, Biswasa D, Chitmeb HR, Ratna S, Muchandia IS, Chandra R. Anti-urolithiatic effects of Punica granatum in male rats. J Ethnopharmacol.2012;140(2):234– 238.

[123] Hosseinzadeh H, Khooei AR, Khashayarmanesh Z, Shariaty VM. Antiurolithiatic Activity of Pinus Eldarica Medw. Fruits Aqueous Extract in Rats. Urol J.2010;7(4): 232-37.

[124] R. Vargas S, R.M. Perez G, S. Perez G, M.A. Zavala S,C. Perez G. Antiurolithiatic activity of Raphanus sativus aqueous extract on rats. J Ethnopharmacol. 1999; 68(1-3):335-8.

[125] Bhavaniamma Vijayakumari, Venkatachalam Sasikala, Singanallur Ramu Radha, Hiranmai Yadav Rameshwar. Rotula Aquatica Lour Aqueous Extract as Anti-Urolithiatic Agent in Experimentally Induced Urolithiatic Rat Model. Int J Pharmacog Phy Res. 2017; 9(4); 553-558

[126] Sujatha Doddola Æ Haritha Pasupulati Æ Bharathi Koganti Æ Koganti V. S. R. G. Prasad. Evaluation of Sesbania grandiflora for antiurolithiatic and antioxidant properties. J Nat Med. 2008;62(3):300-7.

[127] Patel PK, Patel MA, Saralai MG, Gandhi TR. Antiurolithiatic effects of *Solanum xanthocarpum* fruit extract on ethyleneglycol- induced nephrolithiasis in rats. J Young Pharmacists 2012;4:164-70.

[128] R. Anand,G. K. Patnaik,S. Srivastava,D. K. Kulshreshtha &B. N. Dhawan. Evaluation of Antiurolithiatic Activity of *Tribulus Terrestris.* Int J Pharmacog. 32 (3) 2008.

[129] .Hiremath RD, Jalalpure SS. Effect of hydro-alcoholic extract of *Vernonia cinerea* Less. against ethylene glycol-induced urolithiasis in rats. Indian J Pharmacol 2016;48:434-40.

[130] Haiying zhang, ning li, kun li, peng li. Protective effect of Urtica dioica methanol extract against experimentally induced urinary calculi in rats. Mol Med Rep. 2014;10(6):3157-62.