Chapter 2

Review of literature

Kidney stone formation or urolithiasis is a complex process that results from a succession of several physicochemical events including supersaturation, nucleation, growth, aggregation, and retention within the kidneys. Epidemiological data have shown that calcium oxalate is the predominant mineral in a majority of kidney stones. Kidney stones have afflicted many famous historical figures, including Benjamin Franklin, Isaac Newton, Peter the Great and Louis XIV. X-rays of Egyptian mummies dating back eight thousand to ten thousand years ago show evidence of stones. Caesar Augustus, the first emperor of the Roman Empire, suffered from various physical maladies including kidney and bladder stones.

2.1 Epidemiology of kidney stones

Urolithiasis is a longstanding medical illness and still a common public health problem. It affects up to 20% of the general population worldwide [13]. In the United States, up to 12% of men and 6% of women will develop a renal stone at some point in life [14]. While in Middle Eastern countries, the lifetime
prevalence of kidney stone is even higher [15]. In India, 12% of the population is expected to have urinary stones, out of which 50% may end up with loss of kidneys or renal damage. Also, nearly 15% of the population of northern India suffers from kidney stones [3] Recurrence rates as high as 50% in 10 years have also been documented [16].

2.2 Composition of urinary calculi

Calcareous stone is the most common type of kidney stone disease. It accounts for upto 80% of all stones [17]. The primary chemical complexes are calcium oxalate (CaOx) and calcium phosphate (CaP). Uric acid (UA) stone represents about 10 – 15% and the other less frequent types of kidney stones are magnesium ammonium phosphate (MAP) or struvite stones, ammonium urate stones, cystine stones, xanthine and other miscellaneous stones (Table 1). There are four main types of kidney stone, each with different causes.

2.2.1 Calcium stones

Calcium stones are formed from calcium and phosphate, or calcium and oxalate. About 70 – 80% of kidney stones are calcium stones. They usually develop in high levels of calcium in the urine. High levels of calcium in your urine can be caused by:

- Some cancers and kidney diseases
- Sarcoidosis (a condition causing inflammation of the lymph nodes and other organs)
- Treatment with thyroid hormones or some diuretics
- Intestinal bypass surgery
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- Genetic factors
- Eating a diet heavy in meat, fish and poultry
- Taking large amounts of vitamin D. High levels of calcium in the urine can be due to parathyroid glands (glands which control how much calcium is in body) are overactive.

2.2.2 Struvite stones

Struvite stones contain magnesium and the waste product ammonia, and are almost always formed after long-term urinary tract infections. Struvite stones are usually large and are usually found in women.

2.2.3 Uric acid stones

Uric acid stones are formed when there is too much acid in urine. They are likely to develop if one had chemotherapy. There are certain conditions which affect the body’s ability to break down chemicals (such as gout), eating a high-protein diet that includes a lot of meat, or some genetic factors that make the condition more likely. About 10% of kidney stones are uric acid stones.

2.2.4 Cystine stones

Cystine stones are rare and are caused by a hereditary condition called cystinuria, which makes the kidneys create unusually high levels of certain chemicals. About 2% of kidney stones are cystine stones.

2.3 Etiology of Renal Calculus

Kidney stone form when there is a decrease in urine volume or an excess of stone forming substances in the urine. Dehydration through reduce fluid intake
### Composition of Urinary Calculi

<table>
<thead>
<tr>
<th>Composition</th>
<th>Percentage of All Calculi</th>
<th>Common Causes</th>
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<tr>
<td>Calcium oxalate</td>
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<td>Hypercalciuria</td>
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<td></td>
<td></td>
<td>Hyperparathyroidism</td>
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<td></td>
<td></td>
<td>Hypoosmolaria</td>
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<tr>
<td></td>
<td></td>
<td>Renal tubular acidosis</td>
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<tr>
<td>Calcium phosphate</td>
<td>15</td>
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<td>Cystine</td>
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<td>Magnesium ammonium phosphate (struvite)</td>
<td>3</td>
<td>UTI caused by urea-splitting bacteria</td>
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<td>Uric acid</td>
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<tr>
<td></td>
<td></td>
<td>Increased urine acidity</td>
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</table>

Table 2.1: Composition of Urinary calculi.
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or strenuous exercise without adequate fluid replacement increases the risk of kidney stones. Obstruction to the flow of urine can also lead to stone formation. A number of different conditions can lead to kidney stones. Kidney stones may occur due to underlying metabolic conditions such as renal tubular acidosis [17] in which the kidneys are unable to excrete acids, Dent’s disease, a rare X-linked recessive inherited condition which leads to kidney diseases [18], Primary hyperoxaluria [19], gout or hyperuricemia [20]. Other conditions associated with an increased risk of kidney stone include genetics, age and sex. Nanobacteria have also been found responsible for formation of kidney stones [21].

2.4 Major theories proposed to explain stone formation and growth

1. Supersaturation: This theory is based on the binding of salts, which occurs after a certain concentration is obtained [7]. If the salt concentration is less, the compound remains in solution. However if salt concentration exceeds, the compound precipitates. Temperature and the pH of a solution also affect solubility.

2. Crystallization or Nucleation: The crystallization or nucleation theory states that when ions or molecules in a dissociated state bind, crystals form. These crystals cluster to form lattice structures. Crystals are nucleated and grow by aggregation. There have been many studies on the possible mechanisms of crystal aggregate formation following the initial nucleation of crystals which is referred to as nucleation theory [22].

3. Reduction of inhibitors: The Inhibitors deficiency theory Inhibitors are substances that modify or alter crystal growth, thus preventing stone formation. Although urine may be supersaturated with a salt, these in-
Inhibitors can prevent stone formation. These molecules work by forming complexes with active surface compounds, which reduces their binding of calcium to oxidate. Urinary inhibitors are involved in the control of these phenomena [23]. Citrate is the most important urinary stone inhibitor. Magnesium, pyrophosphate, nephrocalcin, glycosamine, RNA fragments are other important stone inhibitors. The absence or reduction of these inhibitors can aid in the production of stone formation.

2.5 Pathogenesis of Stones

Urinary stones or kidney stone formed when the normal balance of water, salt, minerals and other things found in the urine changes. On the one hand kidney must play an important role in water conservation, but at the same time, minerals with low solubility need to be excreted. In general renal stone are of different types, and each type of stone has its own group of causes, however, all four types of renal stones share a common pathogenesis that is based essentially upon excessive super saturation of the urine with poorly soluble material. Under supersaturated condition both homogenous and heterogeneous nucleation occurs. As a result crystal growth proceeds small crystals evolve into large crystals. Alternately many small crystals aggregate to form crystal aggregates (Figure 2.1).

Urine saturation can be increased by a deficiency of inhibitors of crystal growth, e.g. citrate, Magnesium, Pyrophosphate, glycosaminoglycans, by dehydration or over excretion of calcium. Tamm-Horesfall protein (THP), a mucopolyprotein secreted in the kidney, acts to reduce formation of aggregates of stone complexes and is found in lower amounts in chronic stone formers. Other studies have found that THP has a dual role as a modifier of crystal aggregation. In solutions with high pH and low concentrations of calcium and THP, THP acts as a
powerful inhibitor of calcium oxalate crystal aggregation. Conversely, solutions with low pH and high concentrations of calcium and THP, favor self-aggregation of THP molecules which lowers their inhibitory activity against calcium oxalate crystal aggregation [24].

Magnesium is usually deficient in stone formers as low magnesium intake has been linked to an increase in kidney stone formation by increasing the solubility of calcium oxalate stones. With an acute onset of kidney stones increasing the magnesium intake to 2 gm/d for 5 days followed by 500 mg twice a day helps to eliminate further stone formation and may act to decrease the size of an existing one. Magnesium should be given in higher doses on a continual basis for those patients who have had more than one episode of nephrolithiasis. Glycosaminoglycans and other semi-synthetic sulfated polysaccharides have been shown to impede urolithiasis by preventing crystal adherence, correction of abnormal oxalate flux, inhibition of crystal growth and agglomeration and prevention of renal tubule damage [25].
2.6 Diagnosis of kidney stones

The diagnosis of a kidney stone can be confirmed by radiological studies or ultrasound examination; urine tests and blood tests are also commonly performed. Clinical diagnosis is usually made on the basis of the location and severity of the pain, which is typically colicky in nature (comes and goes in spasmodic waves). Pain in the back occurs when calculi produce an obstruction in the kidney. Imaging is used to confirm the diagnosis and a number of other tests can be undertaken to help establish both the possible cause and consequences of the stone.

2.6.1 X-rays

The relatively dense calcium renders these stones radio-opaque and they can be detected by a traditional X-ray of the abdomen that includes the Kidneys, Ureters and Bladder - KUB [26]. This may be followed by an IVP (Intravenous Pyelogram) which requires about 50 ml of a special dye to be injected into the bloodstream that is excreted by the kidneys and by its density helps outline any stone on a repeated X-ray. These can also be detected by a Retrograde pyelogram where similar "dye" is injected directly into the ureteral opening in the bladder by a surgeon, usually a urologist. About 10% of stones do not have enough calcium to be seen on standard x-rays (radiolucent stones).

2.6.2 Computed tomography

Computed tomography without contrast is considered the gold-standard diagnostic test for the detection of kidney stones. All stones are detectable by CT except very rare stones composed of certain drug residues in the urine [26]. If positive for stone, a single standard x ray of the abdomen (KUB) is recommended. This gives a clearer idea of the exact size and shape of the stone as
well as its surgical orientation. Further, it makes it simple to follow the progress of the stone by doing another x-ray in the future. Drawback of CT scans include radiation exposure and cost.

2.6.3 Ultrasound

Ultrasound imaging is useful as it gives details about the presence of hydrenephrosis (swelling of the kidney - suggesting the stone is blocking the outflow of urine) [26]. It can also be used to detect stones during pregnancy when x-rays or CT are discouraged. Radiolucent stones may show up on ultrasound however they are also typically seen on CT scans. However, it is sometimes recommend that US be used as the primary diagnostic technique with CT being reserved for those with negative US result and continued suspicion of a kidney stone. This is due to its lesser cost and avoidance of radiation.

2.6.4 Other

In addition to the techniques mentioned, there are some other investigations also which are performed in order to confirm the presence of the stones in the body. These investigations include:

- Microscopic study of urine, which may show proteins, red blood cells, bacteria, cellular casts and crystals.

- Culture of a urine sample to exclude urine

- Blood tests: Full blood count for the presence of a raised white cell count (Neutrophilia) suggestive of infection, a check of renal function and to look for abnormally high blood calcium blood levels (hypercalcaemia).

- 24 hour urine collection to measure total daily urinary volume, magnesium, sodium, uric acid, calcium, citrate, oxalate and phosphate.
2.7 Treatment of kidney stones

2.7.1 Renal calculi

The characteristics of the stones (size, number, location, and composition), renal anatomy, and clinical factors are all considered when selecting a treatment approach for renal calculi.

2.7.2 Simple renal calculi

Simple renal calculi are those with a stone burden of < 2 cm (aggregate diameter) and normal renal anatomy. Most simple renal calculi (80 – 85%) can be treated successfully with shock wave lithotripsy [27]. However, lithotripsy may fail or be less effective when stones are larger, stones are located in dependent or obstructed parts of the collecting system; stones are made up of calcium oxalate monohydrate, brushite, or cystine; the patient is obese or has a body build that inhibits proper imaging; or it is difficult to target the stone for shock wave delivery and subsequent fragmentation [28].

A retrospective comparison of percutaneous nephrolithotomy and shock wave lithotripsy found that as stone burden increased, the number of lithotripsy treatments and ancillary procedures increased, but stone-free rates decreased [29, 30]. Percutaneous nephrolithotomy results in higher stone-free rates and lower retreatment rates than shock wave lithotripsy. Because it is more invasive, however, percutaneous nephrolithotomy is usually reserved for patients in whom shock wave lithotripsy fails or those who are unsuitable for lithotripsy. Ureteroscopy is an increasingly used alternative for treating simple renal calculi because it has similar stone-free rates to shock wave lithotripsy and morbidity is lower than with percutaneous nephrolithotomy. Ureteroscopy is especially attractive in coagulopathic, pregnant, or morbidly obese patients where
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shock wave lithotripsy or percutaneous nephrolithotomy are less effective or contraindicated.

2.7.3 Complex renal calculi

Complex renal calculi include stones > 2 cm, such as staghorn calculi; stones occurring in kidneys with abnormal anatomy; and stones resistant to fragmentation. Recently published guidelines of the American Urologic Association recommend that staghorn calculi should not be treated with lithotripsy because of relatively poor stone-free rates. Ureteroscopy has been used to treat upper tract stones > 2 cm, but stone clearance rates are significantly lower than with percutaneous nephrolithotomy and stones recur rapidly (16% within six months) [31].

For this reason, percutaneous nephrolithotomy is the treatment of choice for most complex renal stones. Combined percutaneous nephrolithotomy and shock wave lithotripsy (sandwich therapy) for complex stones was commonplace in the 1990s, but improvements in percutaneous nephrolithotomy techniques have led to a decline in the need for shock wave lithotripsy [32]. Even the largest staghorn calculi can be cleared percutaneously with the aid of secondary look nephroscopy and multiple access tracts.

The management of lower pole calyceal calculi remains controversial. A prospective randomised multi-centre trial showed that percutaneous nephrolithotomy was better than shock wave lithotripsy in the clearance of lower pole calculi > 1 cm (stone-free rates of 91% vs 21%). However, for lower pole calculi < 1 cm, a recent prospective randomised trial failed to show a statistically significant difference in stone-free rates between the two techniques. Urolithiasis associated with aberrant renal anatomy can present a treatment challenge. All three techniques described above and even laparoscopy have been used to treat calculi
in these situations.

2.7.4 Ureteral calculi

Ureteral calculi most commonly present with symptoms of acute renal colic. If urgent intervention is not needed the patient and clinician must decide whether to intervene or proceed with expectant management. The likelihood of spontaneous passage decreases as stone size increases. An extensive meta analysis found that most ureteral calculi < 5 mm in diameter pass through the urinary tract spontaneously [33]. Spontaneous passage usually occurs within four weeks after the onset of symptoms [33]. If a stone has not been passed within four weeks, intervention is indicated, as the risk of complications such as ureteral stricture and renal deterioration increase. Therefore, observation is adequate for stones < 5 mm if symptoms can be controlled and follow-up is ensured. For the purposes of selecting treatment, ureteral calculi can be divided into categories on the basis of location.

2.7.4.1 Proximal ureteral calculi

Several endourological options are available for the treatment of proximal ureteral stones: shock wave lithotripsy with or without stone manipulation, ureteroscopy, and percutaneous nephrolithotomy. In 1997, the ureteral stones guidelines panel of the American Urologic Association recommended shock wave lithotripsy as the treatment of choice for stones in the proximal ureter, with stone-free rates up to 85%. A retrospective series noted that proximal ureteral stones > 1 cm have poor stone-free rates with this treatment [34]. However, flexible ureteroscopy is increasingly popular as primary treatment for proximal ureteral stones as a result of the availability of small diameter flexible ureteroscopes, ureteral access sheaths, holmium laser lithotripsy, and stone baskets. Percutaneous
2.7.4.2 Distal ureteral calculi

Although the likelihood of spontaneous passage of stones is highest in the distal ureter, intervention with ureteroscopy or shock wave lithotripsy is often necessary. Both techniques are excellent options for symptomatic ureteral calculi < 1 cm. Randomised controlled trials comparing the two techniques have reached conflicting conclusions [35]. Unlike shock wave lithotripsy, ureteroscopy is not influenced by stone size and can be used to treat distal ureteral calculi > 1 cm. Semirigid ureteroscopy has a success rate of 90–99% for treating distal ureteral stones. Ureteroscopy may also be the simplest solution in institutions with limited access to a lithotripter.

2.8 Prevention and management of kidney stones

There are many preventive strategies available for kidney stones. Main strategies include improved dietary habits. A diet low in protein, nitrogen and sodium is usually advised. Adequate levels of calcium and oxalate are also taken care of. Oxalate rich foods, such as chocolate, nuts, soybeans, rhubarb and spinach are avoided [36]. However, an adequate intake of dietary calcium is also advised. In case of formation of kidney stones, drugs such as thiazides, potassium citrate, magnesium citrate and allopurinol are taken depending on the cause of stone formation.

Most kidney stones do not require surgery and pass on their own. Surgery is necessary when the pain is persistent and severe, in renal failure and when there is a kidney infection. Most simple renal calculi (80–85%) can be treated successfully with shock wave lithotripsy [27]. However, lithotripsy may fail or be less effective when stones are larger; stones are located in dependent or ob-
structured parts of the collecting system; stones are made up of calcium oxalate monohydrate, brushite, or cystine; the patient is obese or has a body build that inhibits proper imaging; or it is difficult to target the stone for shock wave delivery and subsequent fragmentation [29, 30, 28]. A retrospective comparison of percutaneous nephrolithotomy and shock wave lithotripsy found that as stone burden increased, the number of lithotripsy treatments and ancillary procedures increased, but stone-free rates decreased [27, 30, 29]. Percutaneous nephrolithotomy results in higher stone-free rates and lower retreatment rates than shock wave lithotripsy [27]. However, in case of coagulopathic, pregnant, or morbidly obese patients shock wave lithotripsy or percutaneous nephrolithotomy are less effective or contraindicated. Further, a single retrospective study in the USA, at the Mayo Clinic, has suggested that lithotripsy may increase subsequent incidence of diabetes and hypertension [9] (Figure 2.2).

2.8.1 Expulsive theory

This treatment comprises the use of drugs to help the spontaneous passage of ureteral calculi. Several drugs including calcium channel blockers (nifedipine), steroids, and $\alpha$ adrenergic blockers have recently been investigated [34, 35]. The rationale for using $\alpha$ blockers is based on the presence of large numbers of $\alpha_1$ adrenoceptors in the distal ureter. These blockers inhibit basal ureteral tone and peristaltic frequency and decrease the intensity of ureteral contractions.

2.8.2 Other treatments

Certainly and increased oral fluid administration is in order unless there is a blockage of the ureter or kidney. Then, surgical, laser or shock wave intervention is in order to dislodge the stone. For the passage of smaller stones, hot packs over the affected flank helps to relax tense muscles form pain and spasm, allowing
Figure 2.2: Evaluation and management of a patient with kidney stones.
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easier passage of the stone. These can be left in place for considerable periods as long as they are wet packs and are not extracting moisture from the skin. Caution should be taken in the elderly and diabetics as they are less sensitive to heat and burning of the skin may ensue. Increased fluid intake helps pass most stones which are 5 mm or less in size. An initial abdominal x-ray is obtained in order to locate the stone and measure its size. This helps in making management decisions initially as larger stones may need surgical or ESWL therapy.

ESWL therapy is most effective with stones measuring 5 mm up to 2 cm but begins to lose its effectiveness the larger they become. Struvite stones, depending upon the location and size may need surgical intervention, especially if they are causing renal impairment. While ESWL has had some success in eliminating stones there has been some concern that it has limitations in the pediatric population and that its role needs to be redefined. In a study examining ESWL's role in pediatric nephrolithiasis, surgery was ultimately needed in a large number of cases following treatment[37]. Despite the widespread clinical use of ESWL, the margin of safety for the kidney during shock wave application is largely unknown. In a study done on rabbits, dose-dependent moderate damage (subcapsular hemorrhage, interstitial hemorrhage, capsular tension and perirenal hemorrhage) were noted in all kidneys at 24 hours following treatment. Evidence of permanent changes (some fibrosis, tubular and glomerular damage, chronic inflammatory alterations) was noted in long-term follow up, while a complete necrosis of the treated kidney was not encountered [38].

While ESWL is often the first choice of therapy its limitations are also well established: silent calyceal stones, calyceal diverticula stones, nephrolithiasis in horse-shoe kidneys, medullary sponge kidney, and residual fragments after ESWL. Other methods and further refinement of ESWL are currently being examined to decrease morbidity and the need for further invasive treatments.
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For smaller stones less than 5 mm, medical management is usually all that is necessary. Increasing the fluid intake and alkalizing the urine, if it is acidic, or acidifying it if it is alkaline, help to make the stone more soluble and easier to pass. Demulcents such as Althea or Ulmus, coupled with a mild diuretic such as Galium or Zea mays also are useful. An anti infective such as Uva ursi or Barosma added also help to decrease the risk of infection. In cases where there is severe colic from passage of the stone certain homeopathic preparations can help in alleviating the pain and with passage. Dioscorea administered in drop doses along with Piscidia and Belladonna will help with pain relief. Hot packs to the affected flank is also useful for pain relief and ureteral dilation.

2.9 Phytotherapy

Phytotherapy is the study of the use of extracts from natural origin as medicines or health-promoting agents. Although regarded as "alternative medicine" by much of Western medicine, phytotherapy, when critically carried out, is an important field of pharmacognosy Out of the total 4, 22, 000 flowering plants reported from the world [39], more than 50,000 are used for medicinal purposes. In India, more than 43% of the total flowering plants are reported to be of medicinal importance. Utilization of plants for medicinal purposes in India has been documented long back in ancient literature [40]. However, organized studies in this direction were initiated in 1956 [41] and off late such studies are gaining recognition and popularity due to loss of traditional knowledge and declining plant population. Right from its beginning, the documentation of traditional knowledge especially on the medicinal uses of plants, has provided many important drugs of modern day [42, 43]. Even today this area holds much more hidden treasure as almost 80% of the human population in developing countries is dependent on plant resources for healthcare [44].
2.9.1 Herbal treatment of kidney stones

Herbal medicines have long played a role in the treatment and relief of nephrolithiasis. Used singly or in combination they act to increase diuresis, relieve pain and relax muscle spasm which often accompanies passage. While many herbal medicines affect the formation of kidney stones in some way, only a few exhibit a primary action for the condition. The beneficial effects caused by many herbal infusions on urolithiasis can be attributed to a disinfectant action as well as to the presence of saponins. Some solvent action with respect to the disrupting the formation of uric stones is primarily due to their capacity to alkalize the urine[45]. In herbal treatment of kidney stones, antilithics are used to “dissolve” the stones or aid their passing to guard against further retention. Diuretic action is also needed to increase the amount of fluid going through the kidneys and flush out the deposits.

Previous clinical studies have shown that herbal medicines and their concoctions could be used to inhibit calcium oxalate crystallization. However, the pharmacodynamics and in vitro effects of such medicines have not been established. Five Chinese herbal medicines were selected based on their usefulness in treating stones disease [46]. Phytotherapy can reduce the recurrence rate of stones. The use of plant products with claimed uses in the traditional systems of medicine assumes importance. An excellent account of the ‘Pashanabheda’ group of plants, claimed to be useful in the treatment of urinary stones is given by Narayana Swami and Ali [47] and Mukerjee et al. [48]. In India, in the Ayurvedic system of medicine, Pashanabheda is the Sanskrit term used for a group of plants with diuretic and antilithiatic activities (Pashana = stone; Dheda = break).
2.9.2 Plants and plant products with antilithiatic activity

The marketed composite herbal formulations, Cystone (Himalaya Drug Company, India), Calcuri (Charak Pharmaceuticals, Bombay, India) and Chandraprabha bati Baidyanath, India) have been widely used clinically to dissolve urinary calculi in the kidney and urinary bladder. Pharmacological and clinical studies carried out on a composite herbal formulation, Trinapanchamool consisting of five herbal drugs namely Desmostachya bipinnata, Saccharum officinarum, Saccharum munja, Saccharum spontaneum and Imperata cylindrica was found to be effective both as prophylactic in preventing the formation and as curative in dissolving the preformed stones in albino rats. The antilithiasis activity of this formulation has been attributed to its diuretic activity [49].

A study was undertaken to evaluate the in vitro Antilithiatic activity of aqueous extract and sodium hydroxide extract of seeds of Dolichos biflorus as therapy for lithiasis. The ethanol extract of Asparagus racemosus was more active than the methanol and distill water extract of the same plant. The combination of the two plants was not as active as the individual extract [50]. The seeds of Dolichos biflorus and rhizomes of Bergenia ligulata were also tested for their in vitro antilithiatic and anticalcification activity by the homogenous precipitation method. The extracts were compared with an aqueous extract of cystone (a marketed preparation) for their activities. Also a combination of the extracts of the two plants was tested. Extracts of Dolichus biflorus showed activity almost equivalent to cystone while Bergenia ligulata showed less activity and the combination was not as active as the individual extracts [51]. In vitro studies in which calcium oxalate precipitation was induced by addition of 0.1 M sodium oxalate to unfiltered urine samples from Wistar rats and normal humans in absence and presence of Phyllanthus niruri extract (0.25 mg/ml), suggested that extract may interfere with early stages of stone formation [52].
Phyllanthus niruri has an inhibitory effect on crystal growth in rat model of urolithiasis induced by introduction of calcium oxalate seed in bladder of rats. The effect may be due to higher levels of glycosaminoglycans incorporated into calculi [53].

Investigations on the effect of Ammi visnaga seeds on kidney stones revealed that the antilithiatic effect is mainly because of highly potent diuretic activity and amelioration of uraemia and hyperbilirubinemia by seeds of Ammi visnaga [54]. Cranberry juice has antilithogenic properties as its ingestion significantly and uniquely altered urinary risk factors causing decreased excretion of oxalate and phosphate while increase in citrate excretion was noted [55]. C. peltata root powder decreased urinary oxalate, calcium, serum potassium likewise increased serum magnesium levels [56]. The effect of ingestion of 3 and 10 g of tamarind pulp (Tamarindus indica) was studied in normal subjects and in stone formers. Tamarind intake at the dose of 10 g showed significant beneficial effect in inhibiting spontaneous crystallization in both normal subjects and in stone formers [57].

Studies on the stem juice of Musa paradisiaca were found to be effective in dissolving the phosphate type of stones in albino rats induced by foreign body insertion method using zinc discs [58]. In another experimental study stem juice of Musa significantly reduced the incidence of oxalate urolithiasis by lowering the activity of the enzyme glycolic acid oxidase [59]. The stem juice of Musa reduced urinary oxalate, glycolic acid, glyoxylic acid and phosphorus excretion in hyperoxaluric rats. Grases and co-workers of Division of Urochemistry, Department of Chemistry, University of Balaeric Islands, Spain have studied the antilithiatic activity of Zea mays, Rosa canina, Herniaria hirsuta and Agropyron repens in rats. The antilithiatic activity of Zea mays has been assigned to its diuretic activity [60]. Rosa canina was found to have significant activity on cal-
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cium oxalate urolithiasis as it decreased calcuria and increased citraturia [61]. The antilithiatic activity of *Herniaria hirsuta* has been assigned to increase in citraturia [62] where as *Agropyron repens* did not show any positive effects on the risk factors of urolithiasis. The effect of *H. hirsuta* on the adhesion of calcium oxalate monohydrate crystals to renal cells was studied which indicated that *H. hirsuta* altered crystal adhesion only under conditions of increased fluidity [63].

2.9.2.1 Tamarindus indica

*Tamarindus indica*, belongs to the Dicotyledonous family Leguminosae Sub Family Caesalpiniaceae, which is the third largest family of flowering plants with a total of 727 genera and 19,327 species. *Tamarindus indica* is a tropical evergreen tree native to fertile areas throughout Africa and Southern Asia. It is widely cultivated as an ornamental tree and for its acidic fruits used in making drinks and a popular component of many decoctions used as health remedies. In Northern Nigeria, the fresh stem bark and fresh leaves are used as decoction mixed with potash for the treatment of stomach disorder, general body pain, jaundice, yellow fever and as blood tonic and skin cleanser (Table 2.2).

*Tamarindus indica* contain high levels of crude protein [64]. *Tamarindus indica* is also high in carbohydrate, which provides energy, rich in the minerals, potassium, phosphorus, calcium and magnesium. *Tamarindus indica* can also provide smaller amounts of iron and vitamin A. The fruit pulp is the richest source of tartaric acid (8 – 18%) and seeds are rich of valuable amino acid [65]. The plant has a great phytochemical significance. On literature survey it was revealed that a variety of secondary metabolites have been reported from tamarind. The leaf oil contains thirteen components among which linonene (24.4%) and benzyl benzoate (40.6%) were most predominant [66]. The volatile constituents of the fruit pulp were furan derivatives (44.4%) and carboxylic acid (33.3%) of the total volatiles [67]. The major fatty acids of seeds were palmitic
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Table 2.2: Classification of *Tamarindus indica*
acids, oleic acid, linoleic acid and eicosanoic acid. Seven hydrocarbons, α-amyrin, campesterol and α-sitosterol were found in the unsaponifiable matter of seed.

The mucilage and pectin, arabinose, xylose, galactose, glucose and uronic acid were also identified [68] (Figure 2.3).

_Tamarindus indica_ is an important food resource for the Thai population. The flower and leaf are eaten as vegetables [69]. _Tamarindus indica_ is a plant widely used in traditional medicine in Africa for the treatment of many diseases such as fever, dysentery, jaundice, gonococci and gastrointestinal disorders [70]. Pharmacological investigations on _Tamarindus indica_ extracts reported them to have antibacterial, antifungal, cytotoxic [70], gastrointestinal [71]. Aqueous extract of seed reduces blood sugar level [72] shows hypolipidemic effect, reduces 14 – 17% of plasma lipid, total lipid, cholesterol, lipoprotein and triglycerides [73, 74]. The seed coat extract has strong antioxidant property, used as additive to food, cosmetic/ pharmaceutical preparations [75]. The fruit also has antimicrobial and antibiotic activity [76].
2.9.2.2 *Terminalia arjuna*

*Terminalia arjuna* is a large tree distributed throughout India. It is a commonly occurring medicinal plant growing as a 20–30 m high tree. In India, plant is found in plenty throughout In sub Himalayan tracts of Uttar Pradesh, South Bihar, Madhya Pradesh, Delhi, Deccan region mainly along riverside, riverlets and ponds. According to Bhava Prakash, as per ayurvedic pharmacology, it is laghu (light) and ruksh (dry) in properties, it has two main tastes kashya (astringent) and tickta (bitter). The virya i.e. the potency of Arjuna is sheet (cool) and vipaka i.e. the post digestive effect of Arjuna is katu i.e. pungent. It is kapha and pitta pacifying, cardiac restorative, helpful in wounds, Tuberculosis and poisoning; good for obesity and urinary disorders (Table 2.3).

It is well recognized in Ayurveda for its various therapeutic values [77] medicinal values of the plants are also well documented in Unani medicine therapies
Terminalia arjuna is known for its various medicinal properties like tonic, anthelmintic, styptic and alexiteric [79]. The bark of Terminalia arjuna is known for treating heart diseases, coronary artery diseases and hypercholesterolemia [11]. The plant has considerable importance as timber and its tannin containing nuts [80]. Polyphenolic contents were reported from Terminalia Arjuna bark [81]. The bark powder of Terminalia arjuna has also been found to improve antioxidant status in the patients of coronary heart disease and these beneficial effects may be related to its high flavonide content [82](Figure 2.4).

It has been well documented that bark extract contains acids (arjunic acid, terminic acid), glycosides (argentine arjunosides I-IV), strong antioxidants (flavones, tannins, oligomeric proanthocyanidins), minerals etc, but not much is known about the specific biological activity of individual constituents of this plant. Few of the active compounds from T. arjuna bark have been isolated and shown to possess antimutagenic and anticarcinoginic activity [83, 84]. Arjunolic acid, a new triterpene isolated from the bark of Terminalia arjuna have been reported
to have antioxidant and cardioprotective activity [85].

Not much antilithiatic properties of *Tamarindus indica* and *Terminalia arjuna* have been explored yet. Thus it was tempting to know their role in management of urolithiasis.