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A REVIEW ON ANTI-UROLITHIATIC ACTIVITY OF MEDICINAL PLANTS

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ABSTRACT

Medicinal plants have been known for millennia and are highly esteemed all over the world as a rich source of therapeutic agents for the prevention of various ailments. The bioactive ingredients that have the therapeutic activity in plants used in traditional practice are mostly unidentified. Substance found in medicinal plants, containing the healing property of plants is known as the active principle. Chemical principles from natural sources have become much simpler and have contributed significantly to the development of new drugs from medicinal plants. Urolithiasis is the condition where urinary calculi are formed in the urinary tract. It is a common disorder estimated to occur in approximately 12% of the population, with a recurrence rate of 70-81% in males, and 47-60% in females. It causes serious health problems such as severe pain, urinary-tract obstruction and infection that adversely affect well-being of individuals. Treatment option includes shock wave lithotripsy (SWL), ureteroscopy, percutaneous nephrostolithotomy (PCNL), and open or laparoscopic stone removal which are costly and painful. Many synthetic drugs like diuretics and narcotic analgesics are being used in treatment of kidney stone but overuse of synthetic drugs, which results in higher incidence of adverse drug reactions have motivated humans to return to nature for safe remedies. An attempt has been made to emphasize on potent indigenous herbs used in treatment of urolithiasis.

Keywords: Medicinal Plants, Urolithiasis, Adaptogenic, Preclinical studies.

INTRODUCTION

Urinary system:

The Urinary System is a group of organs in the body concerned with filtering out excess fluid and other substances from the bloodstream. The Urinary system includes the following;

- Two kidneys responsible for formation of urine.
- Two ureters responsible for the transport of urine to urinary bladder from kidney.
- Urinary bladder temporary store-house of urine and
- Urethra.

The Urinary system works with the other systems of the body to maintain homeostasis. The kidneys are the main organs of homeostasis because they maintain the acid base balance and the water salt balance of the blood [1].

Kidneys:

The paired kidneys are reddish, bean-shaped organs located just above the waist between the peritoneum and the posterior wall of abdomen. Because their position is posterior to the peritoneum of the abdomen cavity, they are said to be retroperitoneal organs. The kidneys are located between the levels of the last thoracic and third lumbar vertebrae, a position where they are partially protected by the eleventh and twelfth pairs of ribs.

a. External anatomy of kidney:

Each kidney is 10-12 cm (4-5 in.) long, 5-7 cm (2-3 in.) wide, and 3 cm (1 in.) thick. The lateral surface of the kidney is convex. The medial surface is concave and has a vertical cleft called the renal hilum. The ureters, renal

blood vessels, lymphatic, and nerves all join each kidney at the hilum. At the top of each kidney is an adrenal (or suprarenal) gland, an endocrine gland that is functionally unrelated to the kidney.

Three layers of supportive tissue surround each kidney, they are:

1. The deep layer, the renal capsule, is a smooth, transparent sheet of dense irregular connective tissue. It serves as a barrier against trauma and helps to maintain the shape of the kidney.
2. The middle layer, the adipose capsule, is a mass of fatty tissue surrounding the renal capsule. It protects the kidney from trauma and holds it firmly in place within the abdominal cavity.
3. The superficial layer, the renal fascia, is another thin layer of dense irregular connective tissue that anchors the kidney to the surrounding structures and to the abdominal wall. On the anterior surface of kidneys, the renal fascia is deep to the peritoneum.

Renal Vein

The renal veins are veins that drain the kidney. They connect the kidney to the inferior vena cava. Because the inferior vena cava is on the right half of the body, the left renal vein is generally the longer of the two. Unlike the right renal vein, the left renal vein often receives the left gonadal vein (left testicular vein in males, left ovarian vein in females). It frequently receives the left suprarenal vein as well.

Renal Artery

The renal arteries normally arise off the abdominal aorta and supply the kidneys with blood. The arterial supplies of the kidneys are variable and there may be one or more renal arteries supplying each kidney. Due to the position of the aorta, the inferior vena cava and the kidneys in the body, the right renal artery is normally longer than the left renal artery. The right renal artery normally crosses posterior to the inferior vena cava. The renal arteries carry a large portion of the total blood flow to the kidneys. Up to a third of the total cardiac output can pass through the renal arteries to be filtered by the kidneys.

Ureters

The ureters are two tubes that drain urine from the kidneys to the bladder. Each ureter is a muscular tube about 10 inches (25 cm) long. Muscles in the walls of the ureters send the urine in small spurts into the bladder (a collapsible sac found on the forward part of the cavity of the bony pelvis that allows temporary storage of urine). After the urine enters the bladder from the ureters, small folds in the bladder mucosa act like valves preventing backward flow of the urine [2].

Fig No. 1 External Anatomy of Kidney

Urinary bladder

The urinary bladder is a hollow, muscular and distensible or elastic organ that sits on the pelvic floor (superior to the prostate in males). The urinary bladder can hold approximately 17-18 ounces (500 to 530 ml) of urine. The outlet of the bladder is controlled by a sphincter muscle. When the bladder fills with urine (about half full), stretch receptors send nerve impulses to the spinal cord, which then send a reflex nerve impulse back to the sphincter (muscular valve) at the neck of the bladder. A full bladder stimulates sensory nerves in the bladder wall that relax the sphincter and allow the release of the urine into urethra [2].

Urethra

The urethra is a muscular tube (approximately 2 inches in females and 8 inches in males) that connects the bladder with the outside of the body. The function of the urethra is to remove urine from the body [2].

b. Internal Anatomy of kidney:

A frontal section through the kidney reveals two distinct regions: a superficial, light red area called the renal cortex and a deep, darker reddish-brown inner region called the renal medulla. The renal medulla consists of several cone-shaped renal pyramids. The base of each pyramid faces the renal cortex, and its apex called a renal papilla points toward the renal hilum. The renal cortex is the smooth textured area extending from the renal capsule to the bases of the renal pyramids and into the spaces between them. It is divided into an outer cortical zone and an inner juxta medullary zone. Those portions of the renal cortex that extend between renal pyramids are called renal columns.

A renal lobe consists of a renal pyramid, its overlying area of renal cortex, and one-half of each adjacent renal column. Together, the renal cortex and renal pyramids of the renal medulla constitute the parenchyma (functional portion) of the kidney. Within the parenchyma, the functional units of the kidney, about 1 million microscopic structures called nephrons are present. Urine formed by the nephrons drains into large papillary ducts, which extend through the renal papillae of the pyramids. The papillary ducts drain into cup like structures called minor and major calyces. Each kidney has 8 to 18 minor calyces and 2 or 3 major calyces. A minor calyx receives urine from the papillary ducts of one renal papilla and delivers it to a major calyx. From the major calyces, urine drains into a single large cavity called the renal pelvis and then out through the ureters to the urinary bladder. The hilum expands into a cavity within the kidney called the renal sinus, which contains part of the renal pelvis, the calyces and branches of the renal blood vessels and nerves. Adipose tissue helps stabilize the position of these structures in the renal sinus.

Fig No. 2 Internal Anatomy of Kidney

Nephrons

A nephron is the basic structural and functional unit of the kidney. The chief function is to regulate water and soluble substances by filtering the blood, reabsorbing what needed and excreting the rest as urine. Nephrons eliminate wastes from the body, regulate blood volume and pressure, control levels of electrolytes and metabolites, and regulate blood pH. Its functions are vital to life and are regulated by the endocrine system by hormones such as anti diuretic hormone, aldosterone, and parathyroid hormone [2].

Each nephron consists of the following Parts:

- ✓ Glomerulus
- ✓ Bowman's capsule
- ✓ Proximal tubule
- ✓ Loop of henle
- ✓ Distal tubule
- ✓ Collecting duct

Fig No. 3 Structure of Nephron

c. Functions of Kidney:

- Regulation of blood ionic composition - The kidneys helps to regulate the blood levels of several ions, most importantly sodium ions, potassium ions, calcium ions chloride ions and phosphate ions.
- Regulation of blood pH - The kidneys excretes a variable amount of hydrogen ions into the urine and conserves bicarbonate ions, which are an important buffer of pH in the blood. Both of these activities help to regulate blood PH.
- Regulation of blood volume - The kidneys adjusts blood volume by conserving or eliminating water in the urine.
- Regulation of blood pressure - The kidneys also helps to regulate blood pressure by secreting the enzyme rennin, which activates the rennin-angiotensin-aldosterone pathway Increased renin causes an increase in blood pressure.
- Maintenance of blood osmolarity - By separately regulating loss of water and loss of solutes in the urine, the kidneys maintain a relatively constant blood osmolarity close to 300 milliosmoles per litre (mOsm/liter).
- Production of hormones - The kidneys produces two hormones. Calcitriol, the active form of vitamin D, helps to regulate calcium homeostasis, and erythropoietin which stimulates the production of red blood cell.

- Regulation of blood glucose level - Like the liver, the kidneys can use the amino acid glutamine in gluconeogenesis, for the synthesis of new glucose molecules. They can then release glucose into the blood to help maintain a normal blood glucose level.
- Excretion of wastes and foreign substances - By forming urine, the kidneys help excrete wastes substances that have no useful function in the body. Some wastes excreted in urine result from metabolic reactions in the body. These include ammonia and urea from the deamination of amino acids, bilirubin from the catabolism of haemoglobin, creatinine from the breakdown of creatinine phosphate in muscle fibers and uric acid from the catabolism of nucleic acids. Other wastes excreted in urine are foreign substances from the diet, such as drugs and environmental toxins.

Formation of Urine [3]:

Urine is formed in three steps: Filtration, Reabsorption, and Secretion.

Filtration It is a largely passive process where a portion of the blood passes from the glomerular bed into the glomerular capsule. The filtrate then enters the proximal convoluted tubule, where tubular reabsorption and secretion begin.

Tubular re-absorption It occurs when the filtrate components move through the tubule cells and return to the blood in the peritubular capillaries. Some of the reabsorption is passive, but the reabsorption of most substances depends on active transport processes.

Tubular secretion It is the reverse process of tubular reabsorption. This process is important for the disposal of substances not already in the filtrate (drug metabolites, etc) and as a way for controlling blood pH.

General characteristics of urine (<http://www.ivy-rose.co.uk>):

Volume: The average, normal volume is approximately 1000 ml to 2000 ml per day.

Physical characteristics of urine

Colour: yellow or amber but can vary considerably with diet

Turbidity: transparent when freshly voided but becomes turbid (cloudy) upon standing

pH: Range from 4.6-8.0, and varies considerably with the diet

Specific gravity: 1.001 to 1.035

Chemical composition of urine

Urine is approximately 95% of water and the other components of normal urine are the solutes that are

dissolved in the water component of the urine. These solutes can be divided into two categories according to their chemical structure (e.g. size and electrical charge).

Organic molecules

These are electrically neutral and can be relatively large

These include:

Urea - Urea is an organic (i.e. carbon-based) compound. It is also known as carbamide. Urea is derived from ammonia and produced by the deamination of amino acids. The amount of urea in urine is related to quantity of dietary protein.

Creatinine - Creatinine is a normal (healthy) constituent of blood. It is produced mainly as a result of the breakdown of creatinine phosphate in muscle tissue. It is usually produced by the body at a fairly constant rate (which depends on the muscle mass of the body).

Uric acid - Uric acid is an organic (i.e. carbon-based) compound. Due to its insolubility, uric acid has a tendency to crystallize, and is a common part of kidney stones.

Other substances/molecules

Example of other substances that may be found in small amounts in normal urine include carbohydrates, enzymes, fatty acids, hormones, pigments, and mucins (a group of large, heavily glycosylated proteins found in the body).

Individual elements: These include,

Sodium (Na⁺) and Potassium - Amount in urine arise with diet and the amount of aldosterone (a steroid hormone) in the body.

Chloride (Cl⁻) - Amount in urine varies with dietary intake (chloride is a part of common salt, NaCl).

Magnesium - Amount in urine varies with the diet and the parathyroid hormone in the body, (parathyroid hormone increases the reabsorption of magnesium in the body which therefore decrease the quantity of magnesium in urine).

Calcium (Ca²⁺) - amount in urine varies with diet and the amount of parathyroid hormone in the body (parathyroid hormone increases the reabsorption of calcium in the body which therefore decrease the quantity of calcium in urine).

Small groups formed from a few different elements:

Ammonium (NH₄⁺) - the amount of ammonium produced by the kidneys may vary according to the pH of the blood and tissues in the body.

Sulphates (SO₄²⁻) - the quantity of sulphates excreted in urine varies according to the quantity and type of protein in the person's diet.

Phosphates (PO_4^{3-}) – amount in urine varies with the amount of parathyroid hormone in the body (parathyroid hormone increases the quantity of phosphates in urine).

Abnormal Constituents of Urine:

Glucose - Recent intake of sugary foods, diabetes m.

Protein - Physical exertion, high protein; hypertension, glomerulonephritis.

Ketone bodies - Starvation, untreated diabetes mellitus

Haemoglobin - Haemolytic anaemia, severe burns

Bile pigments - Hepatitis, cirrhosis, bile obstruction

Erythrocytes - Bleeding due to trauma, kidney stones, infection, cancer

Leucocytes - Urinary tract infection

d. Diseases or disorder of kidney:

Cystitis: Inflammation of the urinary bladder caused by bacteria

Diabetes insipidus: It is the excessive urination of water due to lack of anti diuretic hormone (ADH)

Glomerulonephritis: Inflammation of the glomeruli, is caused by a bacterial infection

Incontinence: It is the ability to control urination. It may be caused by aging, pregnancies, or prostate surgery.

Kidney stones: These are developed in the renal pelvis or calyces. Predisposing factors for kidney stones include dehydration, infection, obstruction, and genetics.

Renal failure: It is the sudden interruption of kidney function due to obstruction, reduced circulation, or kidney disease.

Urinary tract infections: include cystitis and urethritis, caused by bacteria.

Kidney stones formation (Urolithiasis):

Kidney stones (renal lithiasis) are small, hard deposits of mineral and acid salts on the inner surfaces of the kidney. These stones are polycrystalline aggregates composed of crystalloid and organic matrix. These occur when three specific mechanisms are at work:

- ✓ There is an excess of salt in urine that cannot be dissolved and eliminated. So the urine is over saturated with this insoluble substance and crystals begin to form. Under normal circumstances, these crystals would have dispersed and been eliminated in urine.
- ✓ More crystals begin to form that cannot be excreted. They join together and form a strong bond that develops into a stone.

- ✓ The body is unable to inhibit the crystallization of these substances in the urine and the stones continue to form.

Common sites of formation are renal pelvis, calyces and in the bladder. Often many stones are found in kidney [4]. Many times urolithiasis is idiopathic; some risk factors including dehydration, genetics, and excessive intake of calcium, oxalate, or protein are the main cause of urolithiasis. When urinary calculi are quite tiny, they may pass unnoticed with the urine. Often calculi grow too large to pass easily through the urinary tract as well as some stones have rough or sharp edges, it can be quite painful when they pass through the urinary tract.

Fig no.4 Kidney Stone

Kidney stones may contain various combinations of chemicals. The vast majority (75-80%) of the stones from urolithiasis are made from calcium oxalate or calcium phosphate. The rest are made up of uric acid (possibly resulting from gout), struvite (magnesium ammonium phosphate), and cystine (uncommon and most likely a genetic defect) (NIH Publication no.08-2495).

Epidemiology [5]:

The epidemiology of urolithiasis differs according to geographical area in term of prevalence and incidence, age and sex distribution, stone composition and stone location. Such differences have been explained in terms of race, diet and climate factors. Epidemiological surveys have been previously reviewed showing that in economically developed countries the prevalence rate ranged between 4% and 20%. Bladder stones constitute 10–15% of the stone burden in adult and 15–30% in paediatric stone-formers. As living standard increase, particularly in the urban areas of the more affluent developing countries, the incidence of upper urinary tract stones is increasing.

Classification of Kidney Stones [6]:

Kidney stones are broadly classified into calcareous (calcium containing) stones, which are radio-opaque, and non-calcareous stones. On the basis of their composition, stone are classified as shown in the table.

Classification of Kidney stones

Composition	Causative factors
calcium oxalate, phosphate, or both	Metabolic abnormality Idiopathic
Struvite (triple phosphate)	Infection
Uric acid	Hyperuricaemia
Cystine	Hyperuricosuria
Other (Xanthine, indinavir)	--

Calcareous Stones (Calcium Containing Stones):

Calcium stones are mainly responsible for all urinary calculi. Calcium containing calculi can occur as pure calcium oxalates or calcium phosphate but more often the mixture of two.

Calcium oxalate stones:

Calcium oxalate stones are the most common type of urinary calculi and can exist in monohydrate and dehydrate forms, with or without of phosphate. Calcium oxalate stone are radio opaque and usually visible on plain film radiography or non contrast CT [6, 7].

Fig No.5 Calcium Oxalate Stones

The causes of calcium stones are as follows;

Idiopathic hypercalciuria: Hypercalciuria in the presence of normal serum calcium is termed as idiopathic hypercalciuria. Hypercalciuria is defined as a urinary output of greater than 200 mg of calcium in 24-hour period [8, 18].

Hyperoxaluria: Approximately 80-90% of oxalate is synthesized in the liver. An additional 10% to 20% is related to the dietary consumption of oxalate or vitamin C [6, 7, 8]. Hyperoxaluria causes oxalate crystal formation, which combines with urinary calcium to form calcium oxalate stones [7]. There are several causes of hyperoxaluria

- Primary hyperoxaluria, Type 1 - it is caused by deficiency of the enzyme alanine:glyoxalate amino transferase in the liver.
- Primary hyperoxaluria, Type 2 - it is caused by deficiencies of hepatic enzyme D-glycerates dehydrogenase and glyoxylate reductase, which cause increase in urinary oxalate and glycerate excretion.
- Enteric hyperoxaluria occurs in patients with short bowel syndrome or malabsorption.

Hypocitriuria: Citrate is most common and abundant organic anion in human urine, and is a well-recognized inhibitor of stone formation. Hypocitriuria is defined as urinary citrate excretion of less than 320 mg, it is well known risk factor for calcium nephrolithiasis, and has been identified in 20% to 60% of calcium stone formers. Hypocitriuria is seen in 15% to 63% of patients with urolithiasis [7].

Hyperuricosuria: Hyperuricosuria is defined as urinary uric acid excretion of > 600 mg daily. The most common cause of hyperuricosuria is increased dietary purine intake, because uric acid is the end product of purine metabolism. Chronic metabolic acidosis can result in protein metabolism and thus increased excretion of urate and formation of kidney stones [7].

Calcium phosphate stones:

Calcium phosphate is commonly found in association with oxalate in stones. Calcium phosphate stones occur only when the chemical pressure for crystallization is high, and thus they are usually seen in very active stones disease. Pure calcium phosphate stones always associated with renal tubular acidification defects. When the kidney lose some of their ability to lower urinary pH, the resulting higher pH increases the divalent and trivalent forms of phosphate, which causes calcium phosphate super saturation [6].

Fig No.6 Calcium Phosphate Stones

Non-Calcareous Stones:**Struvite stones [7]:**

Struvite stones are composed of magnesium, ammonium and phosphate mixed with carbonate. These stones are formed in urine with a pH of greater than 7.2. These stones can grow very rapidly to form a complete stone cast within the drainage system of the kidney. They are usually associated with urinary tract infections, which change the urinary environment to permit rapid stone growth. Consequently, the stone formed can become very large in size. If left untreated they can cause chronic infection, destroy the kidney, and may result in death.

Fig No.7 Struvite Stones

Uric acid stones:

Usually, uric acid stones are found between 5 to 10% of all stones analyzed in a stone clinic. Uric acid is an end product of metabolism. Generally, these stones are associated with urine pH less than 5.5. Uric acid stones are spherical with a smooth yellow-orange surface and nearly radio graphically transparent unless mixed with calcium crystals or struvite. Approximately 25% of patients with uric acid stone have gout problem. There are three major factors for the development of uric acid stones i.e. Low urine volume, acidic urine pH, and hyperuricosuria. There are many reasons for this build up: genetics, certain medications, obesity, and a diet rich in foods such as organ meats [9, 10].

Fig No.8 Uric Acid Stones

Cystine stones:

These are rare stones occurring 1% of stone patients due to an inherited defect in amino acid transport within the kidney. Cystine is a building block for muscles, nerves and other parts of the body. But in some people who inherit a rare, metabolic condition, called cystinuria, it is also the source of the least common of all kidney calculi i.e. cystine stones.

Cystine stones occur because the kidneys do not reabsorb cystine properly. Excess cystine crystals are found in the urine of affected patients which clumps together to form stones. Patients who are affected tend to be young and develop recurrent kidney stones throughout life [7].

Miscellaneous Stones:

There are some stones which are rarely found in kidneys or urinary tract which are

- Ammonium uric acid calculi
- Dihydroxyadenine stones
- Matrix calculi
- Triamterene stones
- Xanthine stones

Dihydroxylydine and Xanthine stones occur due to deficiency of the enzyme adenine phospho ribosyl transferase and xanthene oxidase. Xanthine stones also occur due to the intake of larger dose of allopurinol. Triamterine stones occur in the patients who are treated with triamterine (potassium-sparing diuretics). Ammonium uric acid stones occur due to urealytic infection which increased urinary uric acid and decreased fluid intake. Matrix stones are rare stones formed heavily infected urinary tract.

SIGNS AND SYMPTOMS:

- Oliguria (reduced urinary volume) caused by obstruction of the bladder or urethra by a stone or rarely simultaneous obstruction of both ureters by two separate stones.
- Postrenal azotemia and hydronephrosis (distension and dilation of the renal pelvis and calyces) can be observed following the obstruction of urine flow through one or both ureters [11].
- Renal Colic- renal colic is caused by peristaltic contractions of the ureter as it attempts to expel the stones. It typically begins in the flank or lower back, often radiating to the groin or in men, to the testes. Pain caused by kidney stones, referred to as renal colic, is often described as one of the strongest pain sensation felt by humans [12].
- Hematuria, pyuria, and dysuria [6].
- Other symptoms include blood in urine, nausea and vomiting, shivers, sweating and fever if there is accompanying infection.

Pathophysiology of Urinary Calculi:

The physical process of stone formation is a complex cascade of events. Kidney stones result from the growth of crystals into stones [13]. The process of stone formation depends on urinary volume; concentrations of calcium, phosphate, oxalate and sodium ions, concentrations of natural calculus inhibitors and urinary pH [14]. High ion levels, low urinary volume, low pH, and low citrate levels favor the formation of urinary calculi.

The pathogenesis of urinary calculi formation is the end result of the following fundamental multi-step physicochemical processes.

Saturation → Super saturation → Nucleation → Crystal aggregation → Crystal growth → Crystal retention → Stone formation

Super saturation:

The central event in stone formation is super saturation. The term super saturation refers to a solution that contains more of the dissolved material than could be dissolved by the solvent under normal circumstances. Super saturation occurs when the concentration of substances forming urinary calculi increases in urine, or urine volume decreases, as well as the absence or reduction in urinary stone inhibitors occurs in urine.

Super saturation depends on urinary pH, ionic strength, solute concentration, and complexation. The level of super saturation of a salt is expressed as the ratio between the actual ion-activity product (AP salt) and the solubility

product (SP salt). The point at which saturation of a solution is reached, and crystallization begins is commonly known as thermodynamic solubility product (K_{sp}).

Urine contains inhibitors of crystallization and can hold large concentrations of solute above the K_{sp}, a metastable state. If the concentration of solute increases further and a point is reached where it cannot be held in solution, this concentration is known as KF, which is the point of formation of product in urine. Thus, super saturation of the urine constitutes a driving force within the solution which can lead to crystallization and trigger a series of pathophysiologic events that include nucleation, crystal aggregation, growth, and attachment to epithelia.

Nucleation:

Urinary super saturation alone cannot explain the formation of urinary stones. Nucleation is the formation of a solid crystal phase in a solution. It is an essential step in the formation of urinary calculi [13]. Nucleation involves the association of crystalloids in solution to form

a sub microscopic particle. There are two types of nucleation; the homogeneous nucleation and the heterogeneous nucleation.

- The homogeneous nucleation results, when the process occurs spontaneously in a pure solution. Because impurities are always present in human urine, the homogeneous nucleation is unlikely to occur *in vivo*.
- Heterogeneous nucleation sites in urine can be epithelial cells, red blood cells, cell debris, urinary casts, other crystals and bacteria. The surfaces provided by the impurities can serve as a nidus in the nucleation process, leading to the heterogeneous nucleation. The heterogeneous nucleation will, generally, occur at a lower super saturation level than that required for the homogeneous nucleation [14]. The nucleation of crystalline components may occur in the lumens of renal tubules, in the basement membranes of tubule cells, or at both sites, perhaps depending on the type of stone.

Crystal Aggregation:

The process in which crystal nuclei bind to each other to form larger particles is called aggregation. The initial nuclei can grow by further addition of desired salts. Aggregation of particles in solution is determined by a balance of forces, some with aggregating effects and some with disaggregating effects. A small inter-particle distance increases the attractive force and favours particle aggregation. Crystal aggregation plays an important role in stone formation.

Crystal Growth: Crystal growth is the next major step of the formation of urinary calculi. In this process atoms or molecules from solution are added to the solid phase of growing crystal in a geometrically precise arrangement. The crystal growth process starts with the nucleation stage. Several atoms or molecules in a supersaturated liquid start forming clusters. Crystal growth is determined by the molecular size and shape, the physical properties of the material, the super saturation levels, the pH of solution, and the defects present in the structure of crystal. The combination of crystal aggregation and crystal growth can explain the genesis of urinary calculi.

Crystal Retention:

Another process that may lead to stone formation is crystal retention. None of the previously discussed elements, i.e. crystal precipitation, growth, and aggregation would result in urinary stone formation if the nucleated crystals were flushed out by urinary flow. Crystal retention is, therefore, a key factor. Crystal retention will result if the crystals grow large enough to be trapped in renal tubules.

Fig No.10 Pathophysiology of Urolithiasis

Role of Oxidative Stress in Urolithiasis:

Reactive oxygen and nitrogen species play significant regulatory roles. They normally occur at steady state levels and are generated when needed. In various pathological conditions, however, there is uncontrolled generation of the reactive oxygen or nitrogen species and/or a reduction in the endogenous antioxidant capacity leading to the development of oxidative stress. Membrane-associated nicotinamide adenine dinucleotide phosphate (NADPH) oxidase is also a major source of reactive oxygen species (ROS) in the kidneys, particularly in the presence of angiotensin II. According to a number of experimental studies, it is also a likely source of Ox-induced superoxide production. Angiotensin II is implicated in causing oxidative stress by stimulating membrane bound NAD (P) H oxidase leading to increased generation of superoxide. TGF- β participates in ROS production through the activation of NADPH oxidase. Hyperoxaluria-induced production of renal lipid peroxides. Oxidative stress followed by renal cell injury and inflammation due to lipid peroxidation. Loss of membrane integrity subsequently facilitates the retention of calcium oxalate crystals and growth of stones in renal tubules.

Role of Promoters and Inhibitors in stone formation:

Urine is having several substances that change or modify the crystal formation [15]. These can further be divided into inhibitors, promoters and complexors. Substances which prevent or reduce the crystallization are called inhibitors. Urinary inhibitors attach to the growth sites on crystals, retarding further growth and aggregation. Inhibitors exert their effects in multiple ways, including inhibition of primary and secondary nucleation and crystal growth and aggregation.

Promoters promote the growth of crystals and facilitate the formation of urinary calculi. It may be possible that a substance may promote one stage of crystal formation such as growth and inhibits another stage such as aggregation.

Certain substances which form soluble complexes with lattice ions of specific crystals decrease the free ion activity of that ion and effectively decrease the state of saturation for that ion system. These substances are known as complexors. Citrate is the potent complexor of calcium in urine and reduces ionic calcium concentration.

DIAGNOSIS:

The diagnostic studies and procedure useful in the evaluation of renal stones are;

Serum: Electrolyte, Ca^{++} , PO_4 , Uric acid, Creatinine and blood urea nitrogen.

Urine:

Urine analysis: Protein may be noted because of the presences of hematuria. Pus cells and bacteria may be seen. Oxalate bodies are often observed in hyperthyroidism, renal tubular acidosis, and hyperoxaluria.

pH : Urinary pH can be measured easily using nitrazine paper. Persistently alkaline urine may be indicative of renal tubular acidosis or may be related to urease-producing organisms.

24 –hour urine: Volume, Creatinine, Oxalate, Citrate, Uric acid and some ions like Na^+ , Ca^{++} and PO_4 .

Blood count: The white blood count increased as a result of complicating infection, if renal function is not adequate, anaemia may be found.

Radiological Investigation:

Sonography: The main advantage of ultrasound is non opaque calculi as well as opaque calculi are detectable and exhibit the same sonographic findings. Patients who are recurrent stone formers and have histories of recurrent urinary tract infections benefit from sonography.

KUB x-ray: It involves low doses of electromagnetic energy to produce a picture of the kidney-ureter-bladder area. This x-ray will reveal kidney stones in these areas.

Ultrasound: It is a diagnostic technique in which high frequency sound waves are passed into the kidney to detect obstruction and changes.

CT scan: This technique is more sensitive than radiography or sonography. CT scan is not only detects the oxalate and phosphate calculi but also struvite, cystine, and uric acid calculi, which are not detected by radiography.

ACT scan: Involves injecting a dye into the body that infiltrate the kidneys and accentuates the images. Using a series of cross-sectional x-rays, the images, made by the dye, make it possible to detect kidney stones.

Intravenous Urography: Intravenous urogram is the standard well accepted test for documenting obstruction and urinary function in acute ureteric colic patients. The examination is relatively inexpensive, safe, and easily performed.

MANAGEMENT OF KIDNEY STONES:**I. Medical Management:****Diet recommendations [16, 17]:****High fluid intake:**

Patients are advised to take maximum intake of fluid within three hours after taking meals, during periods of physical exercises, bed time and once at midnight. Plain water is good enough but potassium rich citrus fruit

juices such as orange, grape, lime, lemon are preferable. Increased fluid intake actually has been demonstrated to have positive effect on two urinary inhibitors, citrate and Tamm-Horsfall protein. Urinary dilution has been found to increase the inhibitory activity of Tamm-Horsfall protein on the calcium oxalate monohydrate crystal aggregation in the urine of the stone formers.

Restriction of animal proteins:

Animal proteins are rich in sulphur containing amino acids such as cystine, methionine, which on oxidation produces sulphate which forms soluble complexes with calcium in the nephron and limits the reabsorption of this cation. High protein intake of animal origin, especially red meat, contributes to hyperuricosuria, hyperoxaluria, hypercitraturia, and hypercalciuria.

Oxalate restriction:

Avoidance of nuts, spinaches, dark roughage, chocolates, tea, and vitamin C with the advice to maintain recommended daily intake of calcium and to ensure that calcium consumption accompanies the ingestion of oxalate rich foods to prevent the absorption of oxalate.

Sodium restriction:

Increased sodium intake may promote a variety of metabolic changes i.e. increase in the urinary pH, calcium and cystine excretion and decrease in citrate excretion. Therefore, patients are advised to avoid high sodium – containing food with restriction of salt in the diet.

Restriction of calcium:

Calcium restriction becomes a very popular recommendation in the past based on the high incidence of hypercalciuria.

Drug therapy [8, 18]:

Generally, 85% of the time, it is possible to spontaneously pass a kidney stone with urination. Stones larger than 6 millimetres will require some form of intervention. Assuming there is no high grade of obstruction or associated infection in the urinary tract, and symptoms are relatively mild, various non-surgical measures can be used to encourage the passage of a stone.

In normal calciuria - Oral administration of potassium citrate increases urine pH and citrate excretion in the urine.

In hypercalciuria - Thiazide diuretics are reserved for patients who have severe hypercalciuria or patients who have mild hypercalciuria and reduce bone mineral density. The hypercalciuric action of thiazide is attributed to enhance calcium reabsorption. In addition, thiazide induced extracellular sodium depletion promotes sodium

and calcium reabsorption in the proximal renal tubule further reducing urinary calcium.

In hypokalaemia - If magnesium loss is a common because of chronic diuretic use, consider potassium magnesium citrate.

In hyperuricaemia or hyperuricosuria – the following were the drugs used.

- **Allopurinol:** It reduces urinary uric acid level and prevent recurrent. Allopurinol is a xanthine oxidase inhibitor that prevents the conversion of hypoxanthine to xanthine, the precursor of uric acid. The drug is also used in patients with gout or hyperuricemia (high serum uric acid levels).
- **Potassium citrate:** It is effective in the treatment of patients who have calcium stones and normal urinary calcium. By providing an alkali load, potassium citrate increase urinary p^H and citrate, thereby increasing urinary inhibitory activity, and perhaps reducing urinary calcium.

In hyperoxaluria - No specific drugs are available to reduce oxalate excretion in the urine.

- Pyridoxine, a cofactor in the alanine-glyoxylate pathway, may reduce production of oxalate by inducing enzyme activity; In an observation study, high intake of vitamin B6 (>40 mg/day) was inversely associated with risk of oxalate stone formation in women.
- Cholestyramine reduces intestinal absorption of oxalate, but no trials have shown its efficacy in preventing recurrent stones.

II. Surgical Treatment [19, 20]: Surgery should be reserved as an option for cases where other approaches have failed or should not be tried. Surgery may be needed to remove a kidney stone. If it

- Does not pass after a reasonable period of time and causes constant pain.
- is too large to pass on its own or is caught in a difficult place
- blocks the flow of urine
- damages kidney tissue or causes constant bleeding
- Has grown larger.

The following equipments were used to remove the stone by surgery.

1. ESWL(Extracorporeal Shock wave Lithotripsy)
2. PNL (Percutaneous Nephrolithotomy)
3. USR (Ureteroscopic stone removal)
4. Open Surgery

Extracorporeal Shock wave Lithotripsy:

Extracorporeal shock wave lithotripsy (ESWL) is the most frequently used procedure for the treatment of kidney stones. In ESWL, shock waves that are created outside the body travel through the skin and body tissues until they hit the denser stones. The stones break down into small particles and are easily passed through the urinary tract in the urine.

Several types of ESWL devices exist. Most devices use either x rays or ultrasound to help the surgeon pinpoint the stone during treatment. For most types of ESWL procedures, anaesthesia is needed. Complications may occur with ESWL, some patients have blood in their urine for few days after treatment. Bruising and minor discomfort in the back or abdomen from the shock waves can occur. Patients are advised to avoid taking aspirin and other medicines that affect blood clotting for several weeks before treatment.

Sometimes, the shattered stone particles cause minor blockage as they pass through the urinary tract and cause discomfort. In some cases, a tube was inserted i.e. stent through the bladder in to the ureter to help the fragments pass. Sometimes the stone is not completely shattered with one treatment, and additional treatments may be needed

Percutaneous Nephrolithotomy (PNL):

This treatment is often used when the stone is quite large or in a location that does not allow effective use of ESWL. In this procedure, a tiny incision is made in the back and creates a tunnel directly into the kidney, using an instrument called a nephroscope. For large stones, some type of energy probe-ultrasonic or electro hydraulic may be needed to break the stone into the small pieces. One advantage of percutaneous nephrolithotomy is that the

surgeon can remove some of the stone fragments directly instead of relying solely on their natural passage from the kidney.

Ureteroscopic stone removal (USR):

Although some stones in the ureters can be treated with ESWL, ureteroscopy may be needed for mid- and lower-ureter stones. No incision is made in this procedure. Instead, the surgeon passes a small fiberoptic instrument called an ureteroscope through the urethra and bladder into the ureter. A small tube or stent may be left in the ureter for a few days to help urine flow. Before fiber optics made ureteroscopy possible, physicians used a similar "blind basket" extraction method. But this technique is rarely used now because of the higher risks of damage to the ureters.

Open Surgery:

Open surgery involves incisions through the patient's flank and into the kidney. The kidneys are cooled down using ice and x-rays are used during the procedure to

locate specific areas and the stone. The arteries in the kidney are identified and isolated away from the surgical region. The surgeon locates the collecting system and retrieves the stone. If the surgeon finds any blockage, this is corrected. The surgery is very invasive and is now restricted to the patients with very large or complex stones that cannot be removed using less invasive measures and for very obese patients.

The procedure is not appropriate for the following patients:

- Those with bleeding or clotting disorders.
- Those with untreated widespread infection.
- Those with severe and chronic kidney insufficiency.

The following are the animal models for urolithiasis

- Diet-induced
- Chemical induced
- Foreign body insertion method
- *In vitro* models

REVIEW OF LITERATURE

Withenia somnifera

Rimple R Patel et al., (2014) studied anti urolithiatic activity of *Withenia somnifera* in ethylene glycol induced urolithiasis in rats. After completion of treatment after 24 hrs urine was collected and blood was collected by retro orbital puncture and kidney histopathology was done. The methanolic extract of withenia somnifera showed increased in urinary volume and PH. All the treated groups showed decrease in calcium, oxalate, phosphate, creatinine, urea, uric acid level in EG induced urolithiasis [21].

Melia azedarach linn

Senthil rajan dharma lingam et al., (2014) investigate the anti urolithiatic activity of the aqueous and alcoholic extracts of *Melia azedarach linn* leaves in calcium oxalate urolithiasis in male albino rats. Treatment with aqueous or ethanol extract (250mg/kg, p.o) significantly reduced the elevated levels of calcium, oxalate and phosphate excretion in urine. The both extracts demonstrate that melia azedarach linn leaves have potent anti urolithiatic activity [22].

Orthosiphon stamineus

Ramesh K et al., (2014) in the present investigation the ethanolic extracts of *Orthosiphon stamineus* leaves have been used. The ethylene glycol used to inducing the urolithiasis in albino rats. The final results shows the ethanolic extracts of plants have good nephroprotective activity when compared with the standard drug. It was proved by analyzing the biomarkers and enzymes level [23].

portulaca oleracea

D.V. Kishore et al., (2013) conclude that the ethanolic extract of *portulaca oleracea* is effective against ethylene glycol and ammonium chloride induced urolithiasis in albino rats [24].

Glochidion velutinum

Thatikonda vijaya et al., (2013) investigate the methanolic extract of dried leaves of *Glochidion velutinum* as a preventive agent in experimentally induced urolithiasis model in rats. The efficacy of 250 and 500 mg/kg GV extract was studied in 0.75% ethylene glycol and 1% ammonium chloride induced urolithiasis for 21 days in rats. The histopathological analysis and other parameters were measured. The results indicating that the dried leaves of GV have antiurolithiatic activity [25].

musa paradisiaca

Tirumala k et al., (2013) investigated the aqueous extract of stem core of *musa paradisiaca* on ethylene glycol and ammonium chloride induced urolithiasis in rats. Phytochemical estimation was done for the presence of phytoconstituents. Dose selection was made on the basis of acute oral toxicity study (200 mg/kg⁻¹, 400 mg/kg⁻¹ body weight) as per OECD guidelines. Oral administration of extract of *musa paradisiaca* for 28 days resulted in significant reduction in urine level, results suggests that the aqueous extracts of stem core of *musa paradisiaca* restored the metabolic changes in ethylene glycol and ammonium [26].

Tecoma stans

Kameshwaran S et al., (2013) investigate the Antiurolithiatic activity of aqueous and methanolic extracts of *Tecoma stans* (AETS & METS) was carried out on ethylene (0.75% v/v) induced urolithiasis in rats. The presented data indicate that administration of AETS METS to rats with experimentally-induced urolithiasis reduced and also prevented the formation of urinary stone forming constituents in urine and renal tissue brought about by T. stans could contribute to its antiurolithiatic property [27].

Solanum virginiam

Krishna mohan chinnala et al., (2013) investigate the ethanolic extract of *solanum virginiam* (20 mg/kg, 400 mg/kg) was administered orally from 1st day for preventive regimen and from 15th day for curative regimen on ethylene glycol induced urolithiasis in rats. Treatment with ethanolic extract of *solanum virginiam* significantly reduced the elevated levels of ions in urine as well as BUN, serum creatinine and serum uric acid level [28].

Bryophyllum pinnatum

Apexa Bhanuprasad Shukla et al., (2014) investigate the anti urolithiatic effect of aqueous extract of leaves of *Bryophyllum pinnatum* on ethylene glycol induced renal calculi [29].

Ajowan

Swamy ranga reddy K et al., (2012) investigate the anti urolithiatic activity of *Ajowan seeds* on ethylene glycol induced urolithiasis in rats. Several parameters like urea, uric acid, creatinine, calcium, potassium in serum analysis and ultra sound scanning are used to assess the activity. The results indicated that the dose 300 mg/kg body weight [30].

Ceropegia bulbosa

Mohd Azaz Khan et al., (2012) investigate the hydro alcoholic extract of leaves of *Ceropegia bulbosa* was used in animal models of urolithiasis [31].

Swertia chirata

Parmar R.K. et al., (2012) investigate the methanolic extract of *Swertia chirata* drug in experimentally induced urolithiasis model in rats. Histopathological analysis also reveals deposition of calcium oxalate crystals and disruption of tubular cells and juxtaglomerular cells. That deposition and disruption were also reduced in rats treated with *swertia chirata* [32].

Hordeum vulgare

Jignesh G. Shah et al., (2011) studied the anti-urolithic potential, the ethanolic extract of seeds of *Hordeum vulgare* was tested in an animal model of urolithiasis. Glycolic acid induced hyperoxaluria in urolithiatic rats. And, there were significant elevated urine output, kidney weight loss and some renal injury markers in glycolic acid induced rats. In vivo antioxidant parameters including lipid peroxidation (MDA), superoxide dismutase (SOD) and catalase (CAT) were also determined [33].

Vediyuppu cheyaneer

Velpandian V et al., (2012) investigate the *vediyuppu cheyaneer* has been widely used in the Siddha system of medicine for various diseases. For the in vivo anti urolithiatic activity on ethylene glycol induced hyperoxalurea rat, the liquid form of *vediyuppu cheyaneer* showed a significant inhibitory effect at 500 mg/kg [34].

Citrus medica Linn

Chavada kalpeshsinh S et al., (2012) investigate the anti urolithiatic activity of FFCM (flavonoids rich fraction of *Citrus medica Linn*) at all dose level significantly prevented the EG induced changes in

calcium, inorganic phosphate, uric acid, oxalate, urea, citrate, mg level, creatinine clearance and oxidative stress. Cystone (750 mg/kg.p.o) was used as standard drug after completion of treatment period of 28 days, 24 hr urine sample and blood were collected. All can be attributed to its diuretic action, decrease in promoters and increase in inhibitors level and antioxidant potential [35].

Musa stem

Prosobh GR et al., (2012) investigated the evaluation of *Musa stem juice* will prevent the development of stones in kidneys against the ethylene glycol induced urolithiasis in rats. The treatment of urolithiasis induced rats by musa tablet also restored all the elevated biochemical parameters (creatinine, BUN, and uric acid) restored the urine PH of normal and increased the urine volume significantly [36].

Leea macrophylla Roxb

Abu Nasim Nizami et al., (2012) investigate the antilithiatic effect of the whole *Leea macrophylla Roxb* ethanol extract in ethylene glycol induced urolithiasis model of rats. The results of this study demonstrated very promising anti-urolithiatic effect *L.macrophylla* extract with preventive and therapeutic treatments [37].

Celosia argentea

Joshi pranav et al., (2012) investigate the effect of *Celosia argentea* in chemically induced urolithiasis in rats. The ethanolic extract of celosia argentea seeds was scientifically evaluated to study anti urolithiatic activity at low dose (500 mg/kg; p.o). At the end of the treatment changes in various physical parameters, promoters, inhibitors, renal function markers in urine and serum sample and Anti oxidant parameters and histopathology of kidneys were observed [38].

Lawsonia inermis L

K.J. kore et al., (2011) investigate the hydro alcoholic extract of *Lawsonia inermis L* leaves (HELI) showed significant antiurolithiatic activity against calcium oxalate-type stones. The results obtained in this study provide evidence for the efficacy of HELI as antiurolithiatic agent [39].

Cynodon dactylon

Abolfazl Khajavi Rad et al., (2011) investigate the preventive effects of hydro alcoholic extract of *Cynodon dactylon* roots on calcium oxalate calculi in rats. *C. dactylon* was able to decrease the body weight of kidneys. Urine oxalate level decreased in nephrolithiatic rats treated with the extract [40].

Lantana camera linn

Mayee R. et al., (2011) investigate the ethanolic extract of *Lantana camera linn* leaves were evaluated for antiurolithiatic activity against 0.75% v/v ethylene glycol and 2% w/v ammonium chloride induced calcium oxalate urolithiasis and for anti oxidant activity against hyperoxaluria induced oxidative stress in rats. The extract administration also decreased the extent of lipid peroxidation and hence enhanced the levels of antioxidant enzymes in kidneys of urolithic rats [41].

Bergenia ciliata

Sarmistha saha et al., (2011) investigate the hydro alcoholic extract of *Bergenia ciliata* standard drug cystone were administered simultaneously at a dose of 150 and 300 mg/kg body weight and absolute organ weight of ethylene glycol (0.75% v/v) for 28 days [42].

Crataeva magna lour.

Suman Kumar mekap et al., (2011) investigate the *Crataeva magna lour.bark* for its anti urolithiatic activity in two conventional models (in vivo) of urolithiasis in rats. The two methods chosen were

lactose (30%) +ethylene glycol (1%) & ammonium chloride (2%) + ethylene glycol (0.75%) induced urolithiasis res. The results shown by the ethanol extract (400 mg/kg bw) group was compared to standard polyherbal drug (cystone: 5 ml/kg) treated group and thus exhibited potent antiurolithiatic activity [43].

Hygropila spinosa

Satish R et al., (2010) investigate the aqueous extract of *Hygropila spinosa* (200 mg/kg) was administered orally from 1st day for preventive regimen and 15th day for curative regimen against the ethylene glycol induced urolithiasis in rats. The *hygropila spinosa* significantly reduced the elevated levels of these ions and proteins in urine. The histological findings also showed after treatment with extract [44].

Coleus aromaticus

Venkatesh G et al., (2010) investigated the Anti urolithiatic of *Coleus aromaticus* in ethylene glycol induced urolithiatic rats. Treatment with hydro alcoholic extract of coleus aromaticus leaves (CALHAE) significantly reduced the cholesterol levels ay 300 & 600 mg/kg and triglyceride levels at 600 mg/kg in urolithiatic rats. Histopathological reports confirmed that chronic administration of CALHAE (300 & 600 mg/kg) diminished the no. of calcium oxalate crystals in kidneys [45].

List of Medicinal Plants used for Urolithiasis

S.No	Plant Name	Family	Part Used	References
1	Adiantum Capillus Veneris	Carryophyllaceae	Whole plant	Ajj Ahmed et al., 2013 [46]
2	Ceropegia bulbos L.	Asclepidaceae	Tubers	Khan et al., 2012 [47]
3	Hypericum perforatum	Hypericaceae	Leaves	Mohsen K et al., 2012 [48]
4	Kigelia pinnata	Bignoniaceae	Fruits	Ravindra K et al., 2012 [49]
5	Lawsonia inermis L.	Lythraceae	Leaves	Kore KJ et al., 2011 [50]
6	Macrotyloma uniflorum	Fabaceae	Seeds	Anantha Krishna Chaitanya D et al., 2010 [51]
7	Plantago Major	Capparaceae	Whole Plant	Sharifa AA et al., 2012 [52]
8	Punica Granatum	Lythraceae	Fruits	Rathod NR et al., 2012 [53]
9	Solanum xanthocarpum	Solanaceae	Fruits	Paras K et al., 2012 [54]
10	Terminalia Chebula	Combretaceae	Fruits	Anil T et al., 2012 [55]
11	Crataeva magna	Capparaceae	Bark	Suman KM et al., 2011 [56]
12	Tridax procumbens L.	Asteraceae	Leaves	Sailaja B et al., 2011 [57]
13	Helianthus annuus	Asteraceae	Leaves	Khan NI et al., 2010 [58]
14	Paronychia argentea	Caryophyllaceae	Aerial Parts	Bouanani S et al., 2010 [59]
15	Moringa oleifera	Moringaceae	Root, wood	Ravindra V et al., 2006 [60]
16	Tribulus terrestris (L.)	Zygophyllaceae	Leaves	Anand R et al., 1994 [61]

Conclusion:

Kidney is the most valuable organ in the body. It eliminates the most of the waste products. I.e., urea, uric acid & ammonia from the body. There are number of disorders in urinary system includes Urolithiasis. Urolithiasis (nephrolithiasis) or kidney stone is formation of urinary calculi at any level of urinary tract. It is estimated that 12% of world population experience renal stone disease with a recurrence rate of 70%-80% in male and 47%-60% in female. It is the 3rd most common affliction of the urinary health care systems are going to become more & more expensive, therefore we have to introduce herbal medicine system in our health care. Herbal drugs & medicinal plants play a vital role in kidney stone diseases. Undesirable effect of the modern medicine has already been overcome by herbal drugs which have delivered the attention of the people towards the herbal medicines. To increase the acceptability & awareness among the people. There is an urgent need to develop trust & faith towards the safters indigenous system by establishing its validity in treatment for stone diseases.

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