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Review Article

Evaluation Of Antilithiatic Activity of Bark Extracts of Breynia Rhamnoide Mull-Arg in Experimental Animals: A Review

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ABSTRACT

Breynia rhamnoides, a lesser-known yet pharmacologically potent medicinal plant from the family Phyllanthocin, has recently drawn increasing scientific attention due to its broad spectrum of biological activities and ethnomedicinal relevance. Widely distributed in parts of South and Southeast Asia, it has been traditionally employed in various indigenous healing systems to treat ailments such as fever, wounds, diabetes, liver disorders, and infections. These traditional applications suggest the presence of multiple bioactive compounds, which are now beginning to be investigated through modern pharmacological and phytochemical research. Phytochemical screenings of Breynia rhamnoides have revealed the presence of important secondary metabolites such as flavonoids, alkaloids, phenolics, tannins, saponins, and terpenoids. These constituents are believed to contribute significantly to the plant's observed antioxidant, anti-inflammatory, antimicrobial, antidiabetic, hepatoprotective, analgesic, and wound healing activities. Early studies, primarily conducted in vitro and animal models, support its therapeutic potential across multiple disease pathways. Notably, antioxidant activity is attributed to high phenolic content, while antidiabetic effects may involve insulin-sensitizing mechanisms and enzyme inhibition. Despite these promising pharmacological profiles, comprehensive scientific documentation on Breynia rhamnoides remains sparse. Limited clinical studies, lack of standardized extract formulations, and insufficient mechanistic insights hinder its development into validated herbal therapeutics or modern pharmaceutical agents. This review consolidates current knowledge of its botany, traditional uses, phytoconstituents, and pharmacological

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effects, offering a foundation for future exploration. To harness the full potential of Breynia rhamnoides, further in-depth research is essential, including advanced phytochemical analysis, toxicological profiling, pharmacokinetic studies, and clinical trials. With such efforts, Breynia ryanoids may contribute meaningfully to the fields of ethnopharmacology, natural product-based drug discovery, and integrative medicine.

INTRODUCTION

1.1 Lithiasis

Urolithiasis, derived from the Greek words ‘ouron’ (urine), ‘oros’ (flow), and ‘lithos’ (stone), is a complex urological disorder characterized by the formation of calculi in the kidneys, bladder, and urethra. A condition known as lithiasis occurs when minerals accumulate in the bladder, ureter, renal system, or urinary tract, resulting in the formation of stones or crystals. The formation of kidney stones results from an imbalance between promoters, such as uric acid, and inhibitors, such as magnesium.[1]

Numerous sources indicate that-

- Calcium phosphate and calcium oxalate are responsible for 80% of kidney stones.[2]
- Magnesium ammonium phosphate and struvite make up 10% to 15% of kidney stones. [3,4]
- Uric acid is linked to drugs and causes kidney stones in 9% of cases.[5]
- 1% of stones occur due to cystine or ammonium acid urate.[6]

Calcium oxalate calculi commonly form when the solubility limit of a few calcium salts in urine is exceeded[7]. One of the primary pathogenic events in stone development is the supersaturation of urine with elements that could cause stones, such as struvite, calcium oxalate, uric acid, and cystine[8]. Ancient Sanskrit writings from India, dating back to 3000-2000 BC, include the Susruta Samhita, a surgical textbook on urinary stone removal, and Acharya Charaka's Charaka Samhita, which focuses on urologic diseases. Charaka emphasizes prevention over cure in Ayurvedic medicine, mentioning kidney stone formation, a condition that has persisted for generations and remains prominent today.[9] Kidney stones are formed by mineral crystallization and form a rigid mass, varying in size and location. Common symptoms include high fever, vomiting, frequent urination, abdominal pain, and blood in the urine. In severe cases, blood may appear in the urine alongside pain. Infections can cause fever and chills. Less common symptoms include foul-smelling or cloudy urine, vague stomach pain, burning sensations, rib pain, blood in the urine, dizziness, and repeated urinary tract infections.[10] Urolithiasis affects people of all ages, with males being more likely to develop it than females. Calcium oxalate stones are most prevalent in the age range of 50-60. Kidney stones are more common in young women, but men are more likely to develop them due to their higher muscle mass, leading to higher prevalence rates of kidney stones in men [11] Men are more likely to develop kidney stones due to the pro-stone-forming effects of testosterone and the anti-stone-forming effects of estrogen. Additionally, men may break down tissues faster, leading to more metabolic waste and an increased risk of kidney stones.[12] Estrogen can help prevent calcium stones in the male urinary tract by keeping urine alkaline and raising citrate levels, as the male urinary tract is more complex than the female [13]. Recent surveys show a significant increase in kidney stone disease among women between 1997 and 2002, possibly due to lifestyle factors like obesity. The male-to-female ratio has been shifted from 1.7:1 to 1.3:1, and vegetarians may have a lower risk of kidney stones compared to non-vegetarians. [14] Kidney stones, a prevalent urinary system issue, affect 19.1% of men and 9.4% of women, increasing from 3.2% in 1976-1980 to 8.8% in 2014, linked to obesity and diabetes.[15]

Calculi can cause serious medical issues like blockage, infection, hydronephrosis, and urinary tract bleeding if not diagnosed. Common surgical methods include lithotripsy and high-power laser disruption, but they can cause acute renal damage and decrease renal function if not addressed. Over 80% of urinary calculi are calcium oxalate or calcium phosphate stones, highlighting the global prevalence of lithiasis. Men are more likely to have nephrolithiasis (12%), and both sexes are more likely to develop it between the ages of 20 and 40, according to epidemiological studies.[16]

1.2 History of kidney stone

Urinary stones have a long history, dating back to the Ancient Egyptians. In 1901, E. Smith discovered a bladder stone in a mummy in Egypt. Treatments for stones were mentioned in Egyptian medical writings from 1500 BC[17]. The earliest literary quotations about stone disease were found in the Asutu medical texts between 3200 and 1200 BC. The first descriptions of "cutting for the stone" were found in Hindu and Greek writings. Sushruta, a surgeon from ancient India, wrote a book about over 300 surgical procedures, including perineal lithotomy, in his book Sushruta Samhita.[18] Ancient India recommended a vegetarian diet, medicated milk, clarified butter, and alkalis for treating stone sufferers, with surgery used if unsuccessful, as detailed in Sushruta's works.[19]

Ancient Greeks' Early Observations and Documentation on Urinary Stone Disease

• Hippocrates (460-377 BC) described kidney diseases and bladder stone symptoms.

• Hippocrates' Oath of Medical Ethics for physicians emphasized avoiding stone cutting.

• Litotomy was practiced with perineal incision, and bladder wounds were lethal.[20]

Ammonius of Alexandria, 276 BC, was the first to suggest crushing a stone for removal. He stabilized the stone with a hook and used a blunt-ended instrument to split it. He coined the term "lithotomus" for cutting the stone, but his idea didn't gain popularity.[21]

➢ **Contemporary Developments and Ongoing Research (1980–2025)**

The 20th century marked a paradigm shift in urolithiasis management. The introduction of extracorporeal shock wave lithotripsy (ESWL) in the 1980s revolutionized treatment by allowing non-invasive stone fragmentation.[22] Innovations in ureteroscopy, percutaneous nephrolithotomy, and laser lithotripsy using Holmium: YAG and Thulium fiber lasers have significantly improved stone clearance rates and reduced complications.[23] Contemporary research (2020–2025) focuses on precision medicine, improved laser technologies, and metabolic stone prevention. Thulium Fiber Laser (TFL) has emerged as a superior alternative to Holmium: YAG due to its smaller fiber size, lower retropulsion, and finer dusting capability, especially for hard stones.[24] Additionally, miniaturized PCNL techniques such as Mini-PCNL, Ultra-mini, and Micro-PCNL are increasingly used to manage large renal stones in pediatric and adult populations. Mini PCNL and standard PCNL have similar effectiveness in stone-free rate management, regardless of factors like sex, body composition, location, and stone composition. Mini-PCNL is preferred by endocrinologists due to its high efficacy, low morbidity, and short hospital stay. Standard PCNL is the most morbid option, while RIRS is the safest option with acceptable SFR, low morbidity, and short hospital stay for large renal stones.[25,26] There is also a growing emphasis on metabolic evaluation and dietary management to prevent recurrence. Genetic studies are beginning to identify mutations associated with stone formation, such as in Cystinuria, opening doors to targeted therapies. [27] The integration of AI and machine learning models is enhancing diagnostic accuracy, improving treatment decisions, and predicting stone composition.[28]

1.3 Human Excretory System

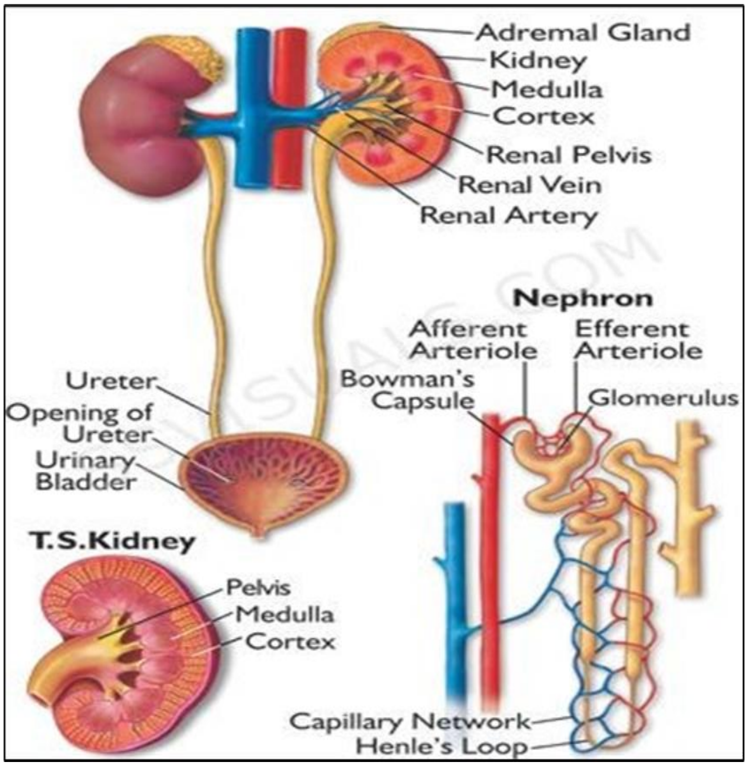

Figure No.1: Human Excretory System

The human kidneys are mesodermal in origin, specifically metanephric, and are essential organs in the excretory system[28]. Typically, there are two kidneys located in the abdominal cavity, each situated on the posterior-dorsal aspect of the abdominal wall in the lumbar region. They are positioned on either side of the vertebral column, spanning from the Level of the T12 to the L2 vertebrae. The right kidney is generally slightly lower than the left, accommodating the liver's position. Each kidney has a characteristic bean shape and a reddish-brown hue. In adults, the average kidney dimensions are approximately 10 cm in length, 5 cm in breadth, and 4 cm in thickness, with a typical weight of about 140 grams, constituting roughly 1% of total body weight. The kidneys are retroperitoneal, meaning they lie between the peritoneum and the dorsal body wall, being covered by the peritoneum only on the ventral side. They are also deeply embedded in adipose tissue, which provides cushioning and protection.[29,30]

1.4 Anatomy of the Kidney

The kidneys are two organs located on either side of the spinal column and behind the peritoneum. They remove excess salt, water, and metabolic waste from the blood while maintaining its pH balance. Positioned in the lumbar, umbilical, hypochondriac, and epigastric regions, they extend vertically from the middle of the third lumbar vertebra to the top margin of the twelfth thoracic vertebra. The left kidney is situated closer to the body's center than the right kidney, and both cross the transpyloric plane. The kidneys are approximately 11.0 cm in length, 6.0 cm in width, and 3.0 cm in thickness, resembling beans in shape. Male kidneys typically weigh around 150 g, while female kidneys weigh about 135 g. They are reddish-brown.[31]

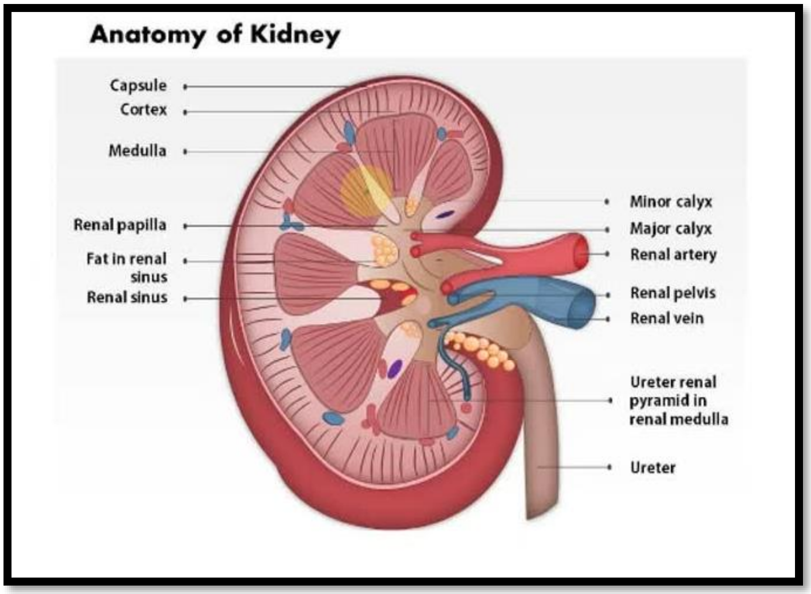

Figure No.2: Inner Structure of the Kidney

The longitudinal section of the kidney consists of two distinct regions: the outer cortex, a dark red area, and the inner medulla, a pale red area.

1. **Capsule**: It is the outermost covering of fibrous tissue that connects the kidney.[32]
2. **Cortex**: The kidney capsule is surrounded by a reddish-brown tissue layer, consisting of kidney corpuscles and convoluted tubules.
3. **Medulla The** kidney is the innermost layer of the body, consisting of renal pyramids separated by renal columns. Each kidney contains 8-18 pyramids, each with a renal papilla at its apex.[33] These papillae project into minor calyces, which form a major calyx. The primary calyces combine to form the renal pelvis, a funnel-shaped structure that collects urine and leads to the ureter.[34] The renal artery enters the kidney through the hilum, generating interlobar, arcuate, and afferent arterioles that supply the glomerular capillaries. The efferent arteriole connects to the peritubular capillaries, forming the vasa recta. The blood veins emerge from the kidney next to the renal artery and the ureter.[35] The kidneys filter approximately 120 liters of plasma daily, 11 times the total extracellular fluid volume, from a 70 kg human. This filtrate is similar to plasma but without protein. 99% of the filtered water and Na+ are reabsorbed, and some substances are secreted into it. Approximately 1.5 liters is voided as urine per 24 hours under normal conditions. Each kidney consists of an outer cortex, inner medulla, and hollow pelvis, which empties into the ureter. The functional unit is the nephron, with approximately 1.4×106 in each kidney, with variation between individuals and age-related decline.[36]

1.5 Function of the kidney

The kidneys are important organs that perform several functions, including:

- The kidney regulates osmotic pressure in the body by regulating fluids and electrolyte balance.
- Metabolic wastes are excreted in the form of urea, creatinine, uric acid, etc., in urine.
- It also regulates PH balance
- Excretion of Drugs and toxins.
- Glucose, amino acids, water, and electrolytes are selectively reabsorbed in the renal tubules.
- It helps in RBC formation.
- Blood pressure regulation.
- The kidneys also produce prostaglandin E and prostacyclin, which have a vasodilator effect and are important in maintaining renal blood flow. The kidneys are important organs that perform several functions, including:

1. **Endocrine function:** Erythropoietin, a kidney hormone, stimulates red blood cell production in the bone marrow, while renin regulates blood pressure.

2. **Osmoregulation:** The kidneys regulate the expulsion of water and electrolytes in urine, thereby controlling the body's salt and water concentration.

3. **Homeostasis:** The kidneys regulate blood pH and remove waste products, excess water, and electrolytes from the body to maintain a stable internal environment.

4. **Excretion:** The kidneys are responsible for filtering blood and eliminating wastes from the body, such as urea, creatinine, and uric acid.

5. **Selective Reabsorption:** The kidneys meticulously resorb crucial molecules like glucose, amino acids, and electrolytes, ensuring their return to the bloodstream.

6. **Erythropoiesis:** Erythropoietin, a hormone produced by the kidneys, stimulates the bone marrow to generate more red blood cells.

7. **Blood pressure regulation:** The kidneys regulate blood pressure by producing hormones like renin, which trigger a series of events that elevate blood pressure.

8. **Secretion of prostaglandins:** Prostaglandins, produced by the kidneys, regulate blood flow, organ function, inflammation, and pain, and are crucial in controlling various physiological processes.[37]

1.6 Renal Diseases

The classification of renal disease can be determined by analyzing five physiological factors.-

1. **Acute renal failure:** Complete or nearly complete kidney failure.
2. **Chronic renal failure:** Impaired kidney capacity due to nephron depletion.
3. **Hypertensive kidney disease:** Caused by glomerular or vascular lesions.
4. **Nephrotic syndrome:** Significant protein loss in urine due to altered glomeruli.
5. **Specific tubular anomalies:** Improper or insufficient reabsorption of specific substances.[38]

➢ **Renal disease can be classified in the following ways-**

- **Acute Renal Failure:** Pre-renal acute renal failure is a condition where blood flow to the kidneys is reduced due to conditions like acute hemorrhage or low blood pressure, such as heart failure with reduced cardiac output, which can result from a malfunction in the system before the kidneys.

- **Chronic Renal Failure:** Uremia, a condition resulting from renal insufficiency, is characterized by anemia and acidosis due to nitrogen retention. It is caused by various renal and extra-renal disorders, including benign nephrosclerosis, polycystic kidney disease, diabetic glomerulosclerosis, chronic nephritic syndrome, and chronic pyelonephritis.[38]

- **Urinary Tract Obstruction:** Obstructive uropathy, also known as kidney and urethral meatus obstruction, affects various parts of the urinary tract, leading to potential pain, infection, renal function decline, sepsis, or even death, especially in certain spots [39]

- **Obstructive Uropathy and Its Impact**

• Obstructive uropathy, also known as obstructive uropathy, affects any part of the urinary tract, including the kidneys and urethral meatus.

• It can cause pain, urinary tract infection, decline in renal function, sepsis, or even death.

• The severity of renal failure and urinary tract obstruction depends on the severity and duration of the obstruction.

• Urine stasis, an increase in the risk of urine infection, can occur when the urinary system is clogged.

• Comprehensive history and physical evaluation are essential for proper patient evaluation. Increased Rate of Renal Calculi

• The incidence of renal calculi is increasing due to changes in diet, lifestyle, obesity, etc.

• In 2012, 10.6% of men and 7.1% of women reported with renal calculi.

• The incidence ratio of renal calculi related to obesity and age is 1.76 for women with a BMI of > 32 kg/m2 and 1.38 for men.

• The prevalence of renal calculi increases with increased intake of caffeinated and sugar-containing beverages.

1.7 Kidney Stone

Kidney stones are formed due to reduced urine output or increased excretion of substances like calcium, oxalate, urate, cystine, xanthine, and phosphate. They grow in the kidney's pelvis and can range in size from microscopic to staghorn stones. The pain is sudden, intense, and radiates from the back, flank, and groin. Risk factors include decreased fluid intake, increased exercise, hyperuricemia, and a history of kidney stones. Most stones pass spontaneously within 48 hours, but some may not.[40]

Factors influencing stone passage include:

- Size of the person
- Prior stone passage
- Prostate enlargement
- Size of the stone
- Pregnancy

Nephrolithiasis, a term for kidney stones, is a stone-forming process with an 80% chance of passage for a 4 mm stone and 20% for a 5 mm stone. If a stone doesn't pass, procedures may be required. The term originates from Greek words for "kidney" and "stone," and is related to renal calculus, a Latin term for stones.[41]

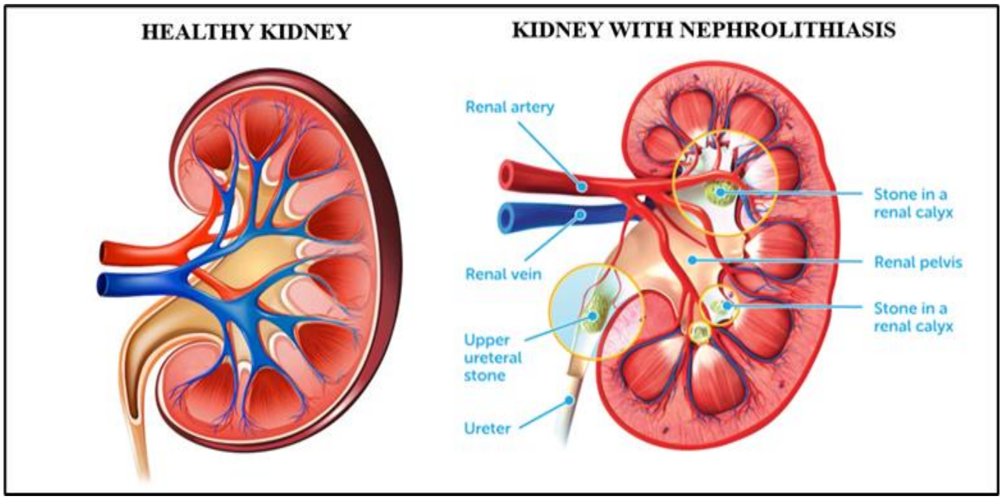

Figure No. 3: Kidney Stone

Both men and women are susceptible to kidney stones, but young men are often at a higher risk than young women.[42] Global warming's effects, primarily in the southeast of the USA, are predicted to increase the number of kidney stones in people's lifetimes from 1.6 million to 2.2 million by 2050.[43]

A) Etiological Factors

Generally, nephrolithiasis is more common in males as compared to females. Mainly six main types of stones are calcium oxalate-containing stone, calcium phosphate-containing stone, cystine-containing stone, uric acid stone, xanthine, and struvite-containing stone. The main causes of nephrolithiasis are hypercalciuria, hyperoxaluria, hypocitraturia, hyperuricosuria, hypomagnesuria, gouty diathesis, etc.

- **Geography:** The global prevalence of kidney stones varies, highlighting the significance of stone belt regions. High temperatures increase perspiration, leading to concentrated urine and higher urinary crystallization, indicating that geography may directly impact the incidence of stone formation.
- **Age and Sex:** The illness affected individuals of all ages, from newborns to seniors over 70, with a 2:1 male-to-female split.
- **History of the family:** A family history of nephrolithiasis increases the likelihood of its occurrence.
- **Nutritional aspects:** Unbalanced diets or food sensitivity can cause urinary changes in stone patients, including hypercalciuria, hyperoxaluria, hyperuricosuria, hypocitraturia, and excessively acidic urine pH.
- **Diet:** Vegetarians are found to have a lower risk of developing stones compared to non-vegetarians, according to certain data.
- **Water intake:** Calculus formation requires a supersaturated urinary environment, leading to stone formation. Increased fluid intake eliminates less supersaturated urine, preventing stone formation.
- **Body weight:** Overweight conditions and obesity were found in 59.2% of men and 43.9% of women. Both of these conditions were strongly associated with an elevated risk of stone formation in both genders due to increased urinary excretion of promoters but

not inhibitors of calcium oxalate stone formation. It was also determined that overweight and obese men are more susceptible to stone formation than overweight women.

- **Kidney stones and other diseases:** People with medical conditions like diabetes, cardiovascular disease (CVD), and essential hypertension are suggested to be at a higher risk of developing kidney stones.

- **Dehydration:** Nephrolithiasis is a condition that increases the likelihood of the excretion of concentrated urine.

- **Hypertension:** Hypertension is linked to an increased risk of nephrolithiasis.

- **Obesity:** The risk of kidney stones increases with an increase in Body Mass Index (BMI).

Inflammatory bowel diseases and gastric bypass surgery influence calcium ion absorption and increase calcium precipitation, leading to nephrolithiasis due to the formation of stone-forming substances.

Drug: Loop diuretics, antacids, acetazolamide, glucocorticoids, theophylline, vitamins D and C, and others have an incidental correlation with the occurrence of renal calculi.

Recurrence: Stone disease recurrence is a common clinical issue, with patients more likely to experience early recurrence due to urinary metabolic abnormalities like low urine volume, hypercalciuria, and hyperoxaluria. Major risk factors include male gender, multiple stones, stone placement, residual fragments, and urinary system abnormalities.

Occupation: The role of occupation in stone formation is a topic of debate. Geographic factors such as Stone Belt residence, lifestyle changes, unhealthy dietary habits, physical manual labor, low socioeconomic status, malnutrition, and reduced fluid intake contribute to kidney-related complications. Some experts suggest that this increased risk may be due to the release of vasopressin, a hormone that increases urine concentration during stress, and other factors.

Molecular Aspects: The role of occupation in stone formation is a topic of debate. Factors like Stone Belt residence, lifestyle changes, unhealthy diets, manual labor, low socioeconomic status, malnutrition, and reduced fluid intake contribute to kidney-related complications. Experts suggest increased risk may be due to vasopressin release during stress.[44]

Types of Kidney Stones

The chemical composition of kidney stones is determined by urine-based anomalies, which affect their size, form, and chemical content. Kidney stones are classified into five categories based on changes in mineral composition.[45]

Figure No. 4: Types of Kidneys Stone

There are four primary types of urinary calculi.

I) Calcium Stones

Calcium stones, which make up about 80% of urinary calculi, are the predominant type of kidney stones. They are primarily composed of calcium oxalate (CaOx) (50% pure), calcium phosphate (5%), and a mixture of both (45%). The main constituent of calcium stones is brushite (calcium hydrogen phosphate) or hydroxyapatite. Calcium oxalate is found in the majority of kidney stones and can be found in the form of CaOx monohydrate (COM), CaOxdihydrate (COD), or a combination of both. Factors contributing to CaOx stone formation include hypercalciuria, hyperuricosuria, hyperoxaluria, hypocitraturia, hypomagnesuria, and hypercystinuria. Urinary pH of 5.0 to 6.5 promotes CaOx stones, while calcium phosphate stones occur when pH is greater than 7.5. Kidney stone disease affects 12% of the global population and is associated with major health concerns such as coronary artery disease and chronic kidney disease. Despite being one of the oldest known and most common diseases worldwide, our understanding of the mechanisms underlying stone formation is lacking. Recent advancements have shed light on the nuanced contribution of diet, environment, genetics, calcium oxalate crystallization, Randall's plaque formation, inflammation, and the recently discovered urinary microbiome. In conclusion, the understanding of kidney stone pathogenesis is limited, and new therapeutic options for preventing and managing this disease will require an improved understanding of the causes of kidney stones.[46]

II) Struvite or Magnesium Ammonium Phosphate Stones

Struvite stones, also known as infection stones or triple phosphate stones, are 10-15% in size and are often caused by chronic urinary tract infections, causing urease production. Urease is needed to convert urea into ammonia and CO2, making urine more alkaline and increasing pH. Phosphate precipitates on insoluble ammonium products, leading to a large staghorn stone formation. Women are more likely to develop this type of stone than men. Struvite stones often form large staghorn calculi, which can obstruct renal function and lead to recurrent infections if not managed properly. Congenital and acquired anatomical abnormalities also contribute to stone formation by impairing urinary drainage and promoting urinary stasis. Medullary sponge kidney, horseshoe kidney, and ureteropelvic junction obstruction are some of the conditions that predispose individuals to recurrent calcium-based stones. Management of such cases requires a combination of medical and surgical interventions.[47]

III) Uric Acid Stones or Urate

Uric acid (UA) stones account for 3-10% of all kidney stones, with diets high in purines, particularly animal protein diets, causing hyperuricosuria, low urine volume, and low urinary pH. Nephrolithiasis is the most common cause, and uric acid stones are more common in men. The prevalence of UA stones increases regularly due to their high correlation with obesity, hypertension, metabolic syndrome, type 2 diabetes, and aging. UA stone formation is mainly due to an acidic urinary pH secondary to impaired urinary ammonium availability. Alkalization of urine is advocated to prevent UA crystallization and is considered an effective therapy. Urology treats urolithiasis, which is prevalent in 5-13% of European countries, 10% in France, and 13% in the U.S. Calcium oxalate is the most frequent component of kidney stones, but UA stones are becoming more frequent, accounting for about 10% of all stones. Factors promoting UA crystallization include an overly acidic urinary pH, hyperuricosuria, and insufficient diuresis. Obesity is the main factor for UA stone formation, responsible for metabolic syndrome and insulin resistance, resulting in decreased ammonia availability and low urine pH.[48]

IV) Cystine Stones

Cystine stones are a rare and often recurrent condition in the urinary tract, accounting for up to 10% of pediatric stone diseases. The two genes responsible for cystinuria are SLC3A1 and SLC7A9. These genes encode the heavy subunit rBAT of a renal b(0,+) transporter, while SLC7A9 encodes its interacting light subunit b(0,+)AT. Mutations in these genes are generally associated with an autosomal recessive mode of inheritance, while SLC7A9 variants result in broad clinical variability even within the same family. Cystine stones are yellowish with a waxy appearance macroscopically and characterized by a flat hexagonal crystal microscopically. They can be distinguished from smooth stones using helical CT in vitro, suggesting that it may be possible to distinguish these stones preoperatively. Cystinuria is a rare cause of urolithiasis, with affected patients having an earlier onset and more aggressive disease than those with other stone types. Current treatment options for cystinuria are limited in their effectiveness at preventing stone recurrence and are often poorly tolerated. Multiple studies suggest that L-CDME is as effective at inhibiting the growth of cystine crystals in vitro as well as *in vivo*. Additionally, the nutritional supplement α-LA prevents the formation of cystine stones, making it a potentially promising therapy for cystine stones. Clinical trials to support the use of these modalities are warranted.[49]

V) Drug-Induced Stones

Kidney stone disease is a long-term, recurrent condition affecting mature and aging men, involving the formation of urinary stones in the kidneys and urinary tract. A rare form, drug-induced urinary stones, accounts for about 1% of all stone types. CT scans predict successful fragmentation during ESWL, and it is a special ADR, classified as a subtype of crystal nephropathy. Diagnosing drug-induced kidney stone disease is difficult due to the possibility of recognizing the condition even after treatment cessation. There are two main types of drug-induced urinary stones: those composed of the drug and/or its metabolites, and those classified as "metabolic stones."[50]

B) Kidney Stone Compositions

Urinary stones are composed of crystals and noncrystalline phases, with the organic matrix consisting of macromolecules such as glycosaminoglycans (GAGs), lipids, carbohydrates, and proteins. The matrix acts as a template for kidney stone assembly, with phospholipids representing about 10.3% of the stone matrix. Brushite stone is a hard phosphate mineral with an increasing incidence rate, and a quarter of calcium phosphate (CaP) patients form stones containing brushite. In the urinary tract, CaP may be present in the form of hydroxyapatite, carbonate apatite, or brushite (calcium monohydrogen phosphate dihydrate, $CaHPO_4 \cdot 2H_2O$). Brushite is resistant to shock waves and ultrasonic lithotripsy treatment. Nephrolithiasis is one of the most frequent urologic diseases. This study aimed to study the composition and frequency of 8854 patient kidney stones and their metabolic risk factors related to their type of calculi. Physicochemical and crystallographic methods were used to assess kidney stone composition. In a subset of 715 patients, 79% of stones were made of calcium salts (oxalate and phosphate), followed by uric acid stones in 16.5%, calcium salts and uric acid in 2%, other salts in 1.9%, and cystine in 0.6%. The male-to-female ratio was almost three times higher in calcium salts and other types of stones, reaching a marked male predominance in uric acid stones. The results show that analysis of kidney stone composition and corresponding metabolic diagnosis may provide a scientific basis for the best management and prevention of kidney stone formation and help study the mechanisms of urine stone formation. A study of 715 patients with kidney stones found that 66.7% had calcium-oxalate (CaOx) as the main composition, followed by uric acid (21%), calcium-phosphate (3%), calcium-phosphate + struvite (2.5%), struvite (2.2%), and calcium oxalate-uric acid (1.0%). Calcium oxalate kidney stones were mainly present in patients with idiopathic hypercalciuria, followed by unduly acidic urine pH and hyperuricosuria (68%). In uric acid stones, unduly acidic urine pH reached 70.6% of the total risk factor diagnosis. Multiple risk factors were observed in 14.7% of calcium-oxalate, 25.0% of struvite, 25.0% of oxalate-calcium phosphate, 11.6% of uric acid stone, and 28.6% of calcium oxalate-uric acid kidney stones. LUV was present in some calcium oxalate stones, uric stones, and calcium phosphate stones. An accurate analysis of kidney stone composition may provide a scientific basis for the best management and prevention of kidney stone formation and help study the mechanisms of kidney stone formation. Physical methods such as X-ray diffraction (XRD) and Fourier transform infrared spectroscopy (FTIR) are currently used for stone analysis. In a series of 8854 consecutive patients, 79.0% were made of calcium salts (oxalate and phosphate), followed by uric acid stones in 16.5%, calcium salts and uric acid in 2.0%, other salts in 1.9%, and cystine in 0.6%.[51]

Types of Stones	Incidence
Pure Calcium Oxalate	33%
Mixed Calcium Oxalate and Phosphate	34%
Struvite	15%
Uric Acid	8%
Pure Calcium Phosphate	6%
Cystine	3%
Artifacts And Other	1%

D) Mechanism of kidney stone formation

Stone-forming crystalloids or substances in urine precipitate out of solution to develop an order for renal stones. The majority of stones, roughly 75% of them, are calcium-based and made of calcium oxalate, calcium phosphate, or a combination of oxalate and phosphate. These mixed stones have multiple components, such as calcium and uric acid accumulation. In susceptible patients, stone formation starts when urine is oversaturated with calcium, cystine, uric acid, struvite, or oxalate. Another 10% of kidney stones are uric acid-based, 1% are cystine-based, and the remainder are mostly struvite-based. Calcium oxalate (CaOx) and calcium phosphate (CaP) accumulate in various stages during the production of calcium stones. The creation of stones is being aided by this process. The process of forming a stone involves the nucleation of the crystals that make up the stone, their growth or aggregation to a size that can interact with an intrarenal structure, their retention within the kidney or renal collecting system, and then additional aggregation and secondary nucleation to form the clinical stone.

- **Different Stages of Stone Formation are as Follows:**

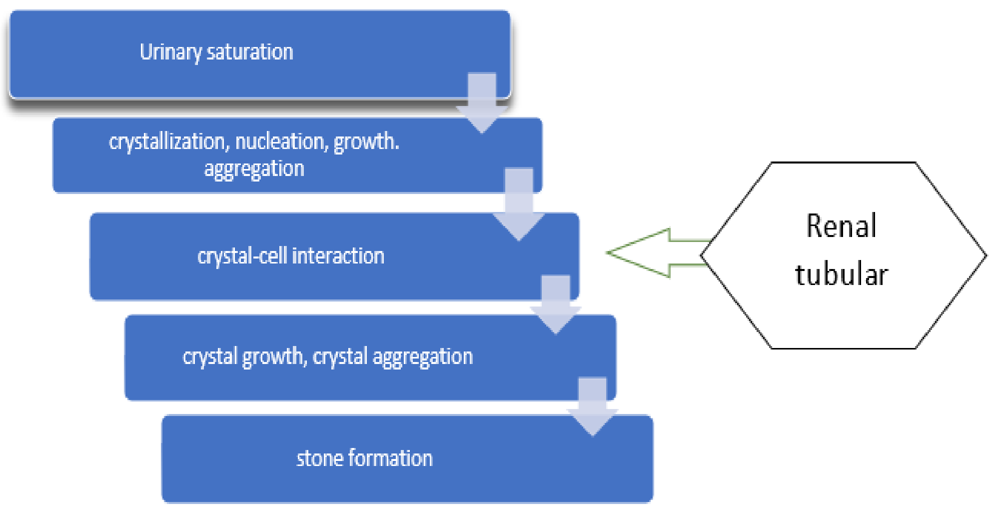

Figure No.5: formation of stone

I) Urinary Supersaturation and Crystallization

Crystal growth in the kidneys is caused by urinary supersaturation, where crystalline particles form. Stone formers excrete millions of urine crystals daily, indicating supersaturation. The 5-10 minute transit time across the kidney makes it insufficient for crystals to form and grow large enough to be caught. Calcium oxalate crystals, which can only grow to a few microns at 1-2 mm/min, are excreted with urine and do not form stones. Urinary components like citrate and magnesium can impact solution supersaturation by reducing free ions by creating soluble complexes with calcium and oxalate.

II) Crystal Nucleation

Nucleation is the initial phase of a supersaturated solution transitioning from the liquid to the solid phase. Stone salts coalesce into loose clusters, which grow as new parts are added. In vitro and in vivo studies show that renal tubular cell damage can facilitate the formation of calcium oxalate crystals by providing building blocks for their heterogeneous nucleation. Membrane vesicles formed during cell decomposition after injury serve as calcium crystal nucleators. In vivo crystals found in renal tubules of hyperoxaluric rats are linked to cellular breakdown products.

III) Crystal Growth

Crystal growth is a process where fresh crystal components are added to a crystal nucleus to reduce total free energy. This process is crucial for particle and stone creation, and crystal development and aggregation play essential roles in every stage of stone development. The crystal surface binding substance in calcium oxalate crystals, formed from human urine, contains human serum albumin, glycoprotein, microglobulin, retinol-binding protein, transferrin, and prothrombin. It is a potent inhibitor of calcium oxalate crystal growth. The rate of crystal growth is low, and the transit time of tubular fluid through the kidney is only several minutes. The probability of a single particle achieving a pathophysiological relevant size through crystal growth alone is extremely low.

IV) Crystal Aggregation

Aggregation is the process by which a small, hard crystal in solution clings together to form a solid, likely causing clinga retention within the kidneys, according to all models of CaOs-Lithiasis, and is considered the most crucial stage in stone production.

➢ **Steps involved in stone formation**

- **Step 1-5**: Homogeneous nucleation begins, then transitions to heterogeneous nucleation, resulting in the formation of oxalate crystals and subsequent redistribution of membrane phospholipids.
- **Step 6**: Oxalate redistributes phospholipid phosphatidylserine in the renal cell surface, causing macrophages to remove and engulf damaged cells, triggering membrane-linked enzyme activity.
- **Step 7**: The cytosolic phospholipase A2 (cPLA2) is a highly attentive phospholipase enzyme that hydrolyzes the acyl group in the sn-2 position of phospholipids. Arachidonic acid and assorted lyso-phospholipids are some of the many byproducts of cytosolic phospholipase A2, which can trigger other signaling pathways in the cell. Arachidonic acid and assorted lyso-phospholipids implicate renal epithelial cell injury. Patients suffering from active renal calculi show elevated plasma and red blood cell membrane arachidonic acid.
- **Step 8-9**: Oxalate exposure in renal epithelial cell culture activates cytosolic phospholipase A2, causing changes in mitochondrial function and gene expression through the byproducts of cPLA2, arachidonic acid, and lysophosphatidylcholine.
- **Step 10-11**: Ceramide generation relies on cytosolic phospholipase A2 activation and oxalate-induced activation, causing membrane damage, injury, proliferation, cytotoxicity, and renal cell damage through signaling molecules.
- **Step 12-15**: Reactive Oxygen Species (ROS) cause cell membrane damage, leading to crystal binding sites being unmasked, forming centers for nucleation of new crystals, which in turn promote stone development. Endocytosis exacerbates cell damage, while crystals may dissolve or re-emerge, further promoting stone growth in the renal interstitium. Oxalate exposure may also leave cellular debris for further crystal growth [52]

1.8 Causes of Lithiasis

A. Dietary Factors

- **High Oxalate Intake:** Consuming foods rich in oxalates, such as spinach, rhubarb, and beetroot, can increase the risk of calcium oxalate stone formation.
- **High Salt (Sodium) Intake:** A diet high in sodium can lead to increased calcium Levels in

the urine, increasing the likelihood of stone formation.

- **Low Fluid Intake:** Inadequate hydration can result in concentrated urine, making it easier for minerals to crystallize and form stones.

B. Metabolic Factors

- **Hypercalciuria:** An excessive amount of calcium in the urine can contribute to the formation of calcium-based stones.

- **Hyperoxaluria:** High Levels of oxalate in the urine can lead to calcium oxalate stone formation.

- **Hyperuricosuria:** Elevated Levels of uric acid in the urine can promote uric acid stone formation.

- **Cystinuria:** A genetic disorder that causes the kidneys to excrete too much cystine, leading to cystine stone formation.

C. Medical Conditions

- **Urinary Tract Infections**: Infections can create an environment conducive to stone formation by altering the chemical composition of urine.

- **Kidney Diseases:** Conditions like polycystic kidney disease can increase the risk of kidney stones.

D. Anatomical Factors

- **Obstruction:** Blockages or structural abnormalities in the urinary tract can hinder the flow of urine, increasing the risk of stone formation.

E. Medications and Supplements

- Certain medications and supplements, such as diuretics and antacids containing calcium, can contribute to stone formation in susceptible individuals.

F. Family History

- A family history of kidney stones may increase an individual's risk of developing them due to shared genetic and environmental factors.

G. Geographical and Climate Factors

- People living in regions with a hot and dry climate may be more prone to kidney stone formation due to increased dehydration [53]

Table No:2 Animal Models for Lithiasis [54,55,56]

Type of approach	Lithogenic agent	Diet/administration	Effects
Cross-breeding	Inbreeding hypercalciuric	Multiple-generation inbred Multiple diets/agents applied	Hypercalciuria Hyperoxaluria CaOx crystals Cap crystals
Exogenous induction	Sodium oxalate Glycolic acid Ethylene Glycol (EG) Hydroxy-L-proline (HLP)	Intraperitoneal injection of 10 mg/kg sodium oxalate Free drinking of water with powdered 3% glycolic acid 0.75% EG in water with/without ammonium chloride, vitamin D, calcium chloride Intraperitoneal injection of 2.5 g/kg HLP Mixed in the	Prompt CaOx crystal deposits Crystal aggregation in the ducts of Bellini Hyperoxaluria Hypocitraturia CaOx crystal deposits Hyperoxaluria CaOx crystalluria CaOx crystal deposits Renal toxicity

		chow of 5% HLP	Hyperoxaluria CaOx crystal deposits are less toxic compared to other agents
Dietary manipulation	Potassium oxalate supplement Magnesium (Mg) deficiency Vitamin B6 (pyridoxine) deficiency	% Level of potassium oxalate Dietary Mg deprivation Dietary intentional deficiency of pyridoxine	CaOx crystal deposits Increase in CaP crystal deposits Hyperoxaluria Hypocitraturia CaOx crystal deposits
Surgery	Intestinal Resection Gastric Bypass Surgery	Resection of the distal 40-45 cm of the terminal ileum Combination diet of high oxalate/low calcium/high lipid fat Roux-en-Y gastric bypass 40% fat and 1.5% sodium oxalate diet	Hyperoxaluria Hypocitraturia CaOx, CaP, $CaCO_3$ crystal deposits Hyperoxaluria CaOx crystal deposits

1.9 Clinical Symptoms of Lithiasis

- Urinary lithiasis, commonly referred to as kidney stones, presents with a range of clinical symptoms that vary based on the stone's size, location, and impact on urinary flow. The degree to which urine flow is obstructed and the intensity of localized tissue reactions are primary determinants of these symptoms.

- **Clinical Symptoms:**

- **Renal Colic:** Characterized by sudden, severe pain in the flank or lower abdomen, renal colic often radiates to the groin, scrotum, or labia. This pain is typically episodic, coming in waves lasting 20 to 60 minutes, and is associated with peristaltic contractions of the ureter as it attempts to expel the stone. Nausea and vomiting frequently accompany this pain.

- **Hematuria:** The presence of blood in the urine, which may be microscopic or visible, occurs in approximately 85–90% of patients with urinary stones. This results from irritation and damage to the urinary tract lining by the stone.

- **Dysuria:** Painful or difficult urination, often accompanied by a frequent urge to urinate, is common, especially if the stone is near the bladder outlet.

- Urinary Retention and Distention: Obstruction can lead to an inability to urinate, causing bladder distention and discomfort. In severe cases, this may progress to anuria (absence of urine output).

- **Urinary Tract Infections (UTIs):** Stagnant urine due to obstruction increases the risk of infections, presenting symptoms like fever, chills, and cloudy or foul-smelling urine.

- **Abdominal Distention:** As the disease progresses, abdominal distention may occur due to urine accumulation behind the obstruction.

- **Rectal Prolapse:** In animals, partial urinary obstruction can lead to rectal prolapse, characterized by the protrusion of the rectal lining through the anus.

- **Behavioral Changes in Animals:** Animals may exhibit signs such as restlessness, kicking at their bellies, or adopting a treading stance due to discomfort. They may also dribble blood-tinged urine after prolonged, painful attempts to urinate.

- **Systemic Symptoms:** Progression of the condition can lead to systemic signs like tachycardia (rapid heart rate), tachypnea (rapid breathing), and uremic breath odor due to the accumulation of metabolic waste products

1.10 Symptoms of Lithiasis

- Severe pain in the side and back, below the ribs.
- Pain that comes in waves and fluctuates in intensity.
- Pain on urination.
- Pain that radiates to the lower abdomen and groin.
- Pink, red, or brown urine.
- Nausea and vomiting.
- Persistent need to urinate.
- Urinating more often than usual.[57]

1.11 Risk factors for kidney stones

In most cases, a definite cause is not found. Kidney stone risk is increased by a risk factors for kidney stones.

- **Family History:** Having a family history of kidney stones significantly increases the risk, with studies indicating that individuals with a first-degree relative who has had kidney stones are at a higher risk of developing them.

- **Insulin Resistance:** Insulin resistance can lead to increased urinary calcium excretion, contributing to stone formation.

- **Hypertension:** High blood pressure has been linked to kidney stone development, possibly due to associated metabolic changes affecting urine composition.

- **Primary Hyperparathyroidism:** This condition leads to elevated calcium Levels in the blood and urine, promoting stone formation.

- **Gout:** Gout results in increased uric acid Levels, which can crystallize and form stones.

- **Chronic Metabolic Acidosis:** This condition alters urine pH, favoring the formation of certain types of stones.

- **Surgical Menopause:** Post-menopausal women who have undergone surgical menopause may have a higher risk of developing kidney stones, potentially due to changes in calcium metabolism.

Kidney stone development in postmenopausal women is linked to hypertension and a magnesium and calcium-deficient diet. Patients with binary tract anatomical shape calcium are more likely to develop stones. About 25 cure stones are idiopathic in origin, and up to 80% of individuals with calcium stones have metabolic risk factors. Many medications also increase the risk of stone disease.[58,59]

1.12 Anatomical abnormalities that increase the risk of stone disease

- Hydronephrotic renal pelvis or calyces
- Calyceal diverticulum
- Obstruction of the pleural junction
- Horseshoe kidney
- Ureterocele
- Vesicoureteral reflux
- Ureteral stricture
- Tubular ectasia (medullary sponge kidney)[60]

1.19 Treatment of kidney stones

Nonpharmacological Approaches:

- By increasing fluid intake by more than 2 liters per day.
- Increasing citric acid intake.
- The recommended intake of calcium is moderate, with limited sodium intake and avoiding supplemental vitamin C.
- Avoiding Oxalate-rich foods.
- Limiting animal protein.
- Limited consumption of soft drinks containing phosphoric acid.
- Magnesium intake reduces the symptomatic effect of nephrolithiasis [61]

Urine Alkalization

- Dietary elements that alkalize the urine include sodium bicarbonate, potassium citrate, Magnesium citrate, and bicitra (a combination of sodium citrate dehydrate and citric acid monohydrate). Increasing the urine pH to 6.5 which aids in the dissolution of uric acid stones. Increasing the urine pH to>7.0 increases the risk for the formation of calcium phosphate stones. Testing with nitrazine paper periodically to ensure the urine pH remains in the optimal range.[62]

1.14 Surgical Treatment

Currently, there are four methods of stone removal

- **Extracorporeal Shockwave Lithotripsy (ESWL)**

- Non-invasive procedure using shock waves to disintegrate kidney stones. Involves placing the patient's care in warm, purified water or a water cushion machine.
- Not ideal for stones larger than 2 cm.
- Other methods include ureterorenoscopy, retrograde intrarenal surgery, percutaneous nephrolithotomy, and open surgery.
- Introduced in Russia in the 1950s, first implemented in humans in 1980.
- Success rates for stones smaller than 2 cm: 70-80%.

Failure rate: 30%-89% after initial session. Identification of suitable candidates can reduce the failure rate.[63]

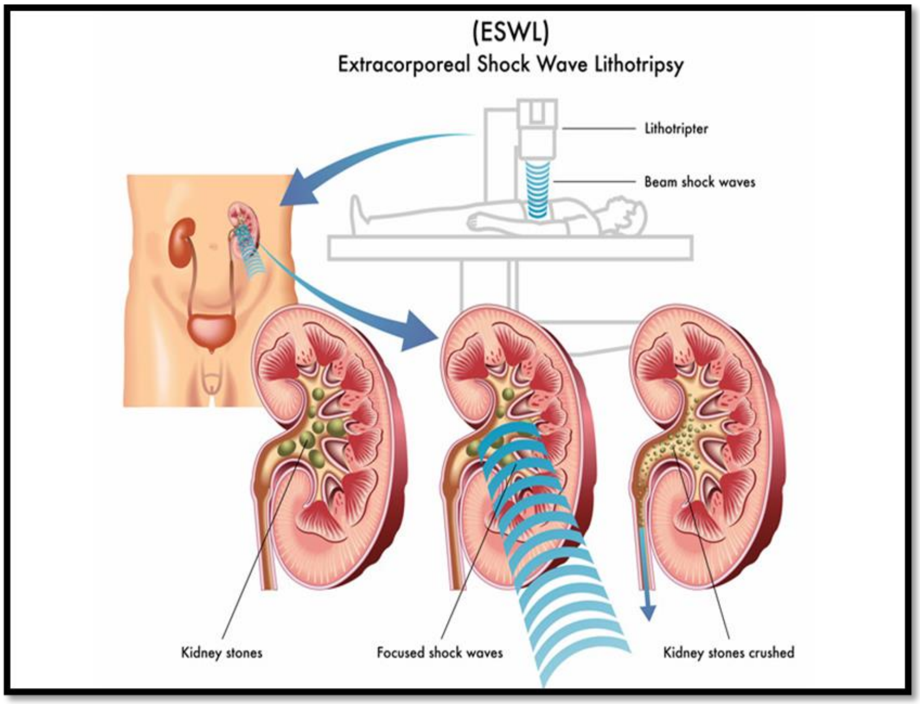

Figure No.6: Extracorporeal Shockwave Lithotripsy

➢ Percutaneous Nephrolithotomy (PCNL)

Percutaneous nephrolithotomy (PCNL) is a procedure used to remove kidney stones from the urinary tract using a nephroscope passed into the kidney through a track created in the patient's back. It was first performed in Sweden in 1973 as a less invasive alternative to open surgery on the kidneys.

- Tubeless PCNL is preferred by endourological urologists due to its improved patient experience and shorter hospital stays.
- Clinical data from 40 cases of conventional PCNL and tubeless PCNL patients were analyzed between December 2023 and April 2024.
- Both groups achieved complete stone clearance (100%).
- The tubeless PCNL group had lower pain scores and shorter hospital stays.
- No significant differences in operative time, renal functional impact, hemoglobin reduction, or inflammatory markers.
- Tubeless PCNL is safe and feasible under these conditions.[64]

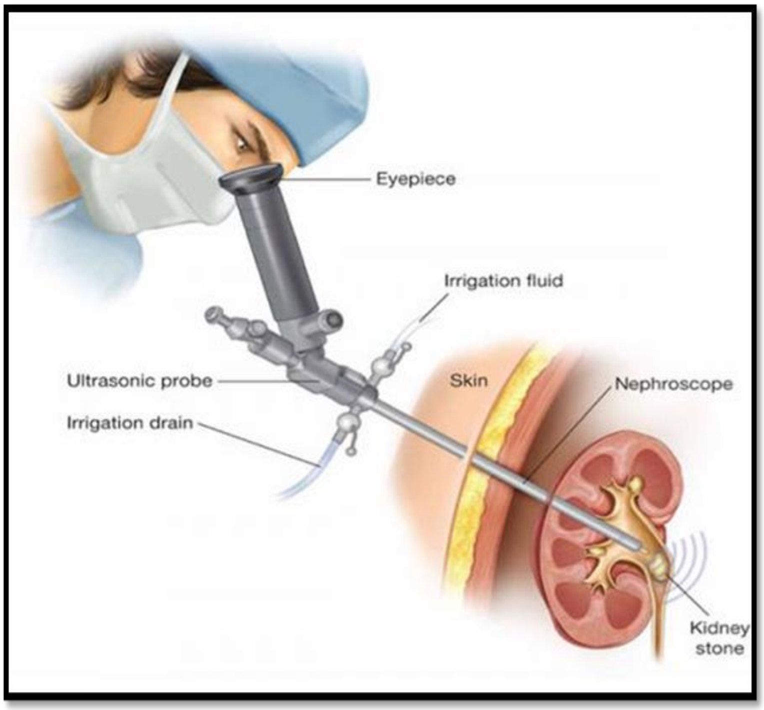

Figure No.7: Percutaneous Nephrolithotomy

➢ **Stone Removal**

Ureteroscopic Stone Removal and Acute Renal Failure

- Ureteroscopic stone removal involves passing a fiber optic instrument through the urethra and bladder.
- The surgeon locates and removes the stone using a cage-like device or a shockwave-producing instrument.
- A tube may be left in the ureter for several days to aid in healing.

Acute Renal Failure (ARF)

- ARF is a critical condition causing a rapid decline in kidney function.
- Types include pre-renal, intrinsic, and post-renal.
- Post-renal ARF is often caused by urinary tract obstructions, with ureteral stones being a common cause.

Obstructive Ureteteral Calculi

- Obstructive ureteral calculi cause severe colic pain.
- Calculus anuria is a medical emergency.
- Urgent decompression of the obstructed tract is prioritized in cases of renal failure, infection, or complete obstruction.
- Ureteroscopy combined with intracorporeal lithotripsy is the preferred approach for most obstructive lower and middle ureteral calculi.[65]

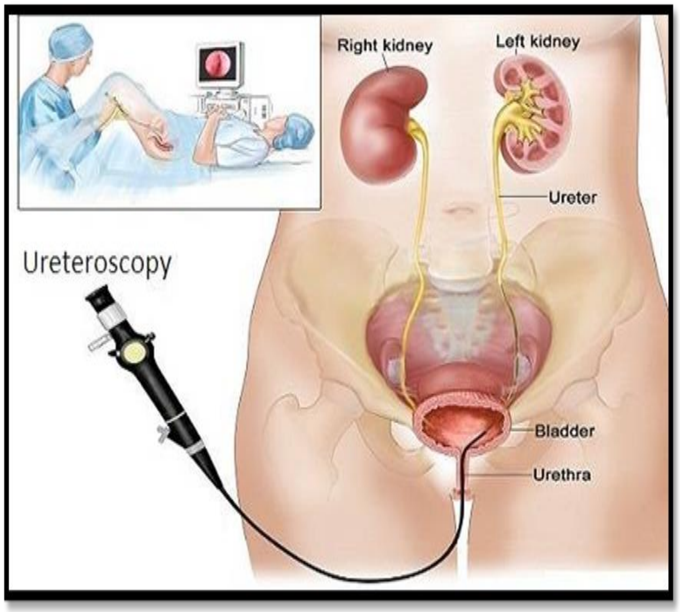

Figure No. 8: Ureteroscopic Stone Removal

- **Open (incisional) Surgery**

➢ **Kidney Stone Removal Procedures**

- Open Surgery and Coupulum Pyelolithotomy.
- Open surgery involves opening the affected area and removing the stone.
- Coupulum pyelolithotomy involves injecting a liquid into the kidney, creating a jelly-like clot to trap the stones.
- Stone extraction is done through an incision in the kidney.

➢ **Complications of Kidney Stones**

- Complex stone burden.
- Failed minimally invasive procedures.
- Comorbid medical conditions.
- Morbid obesity.
- Anatomical abnormalities.
- Ureteropelvic junction obstruction (UPJO).
- Skeleton deformity.
- Nonfunctional kidney (nephrectomy).

➢ **Ureteropelvic Junction Obstruction (UPJO)**

- Common anatomical abnormality in children with hydronephrosis.
- Concurrent renal calculus is common.
- Open surgery is recommended for both pyeloplasty and pyelolithotomy.
- Laparoscopic approach for pyeloplasty in conjunction with percutaneous nephrolithotomy suggested.
- In complex UPJO, a ureterocalicostomy is preferred.
- Concomitant lithotripsy using Shock Pulse lithotripter during laparoscopic ureterocalicostomy is a safe and feasible option[66].

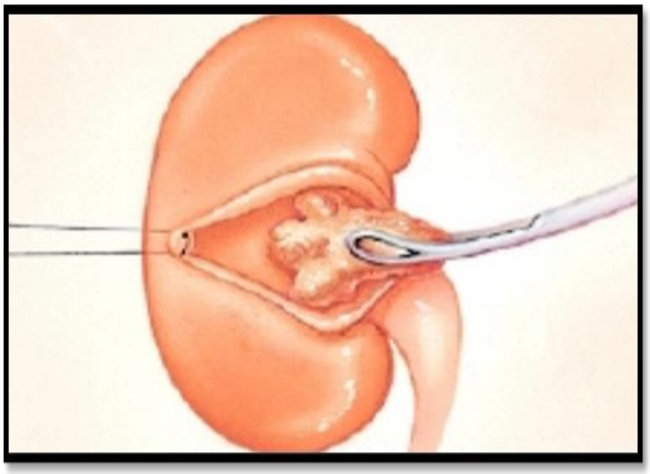

Figure No. 9: Open (Incisional) and laparoscopic treatment

➢ Herbal Treatment

Sr. No.	Herbal drugs	Uses
1.	*Melia Azedarach Linn.*[67]	Traditionally, it is used as an anthelmintic, antilithic diuretic, emmenagogue, astringent, and stomachic.
2.	*Petroselinum Sativum*[68]	Diuretic Properties, Antioxidant Activity, Anti-inflammatory Effects, Alteration of Urine Composition
3.	*Hygrophila Spinosa*[68]	Jaundice and Liver Disorders, Rheumatism and Joint Pain, Renal Stones, Gonorrhea
4.	*Relith*[68]	Antiurolithiatic Activity
5.	*Cucumis Trigonus*[68]	Litholytic Activity, Anti-inflammatory and Antioxidant Properties
6.	*Aerva Lanata And Vediuppu Chunam*[68]	Antiurolithiatic, Diuretic, Antimicrobial, Anti-inflammatory, Antidiabetic, Hyperoxaluria Treatment

In Ayurveda, several medicinal plants and Ayurveda compound formulations have been prescribed by Ayurveda doctors for the treatment of lithiasis.

Plant Profile[69,70]

Figure No. 11: ***Breynia rhamnoide mull-Arg***

Name: *Breynia rhamnoide mull-Arg*

Famlily: Phyllanthaceae/ Euphorbiaceae

Vernacular Names: Hindi: Tikhar

Marathi: Mothi Kangali

Sanskrit: Aruni

Other Names : *B. Vitis-Idaea*, Commonly Known as Coral Berry Tree, Indian Snowberry, Mountain Coffee Bush, Civappu-P-Pula in Tamil, Arauni in Assamese, Bhita Shalapati in Bengali.

Taxonomical Classification

Table No. 2: Taxonomical Classification

Kingdom	Plantae
Subkingdom	Tracheobionta
Super division	Spermatophyta (Seed plants)
Division	Magnoliophyta (Angiosperms - Flowering plants)
Class	Magnoliopsida (Dicotyledons)
Subclass	Rosidae
Order	Malpighiales
Family	Phyllanthaceae
Genus	Breynia
Species	*Breynia rhamnoide*

Habitat: Andaman Is., Bangladesh, Cambodia, China South-Central, China Southeast, India, Malaya, Myanmar, Nicobar Is., Pakistan, Philippines, Sri Lanka, Sumatra, Thailand, Vietnam.

Medicinal Parts: The medicinal part is the dried herb.

Flowers and Fruits:

- The flowers are small, greenish-yellow, and grow in axillary clusters.
- They are unisexual, with male and female flowers occurring on the same plant (monoecious).
- The calyx is cup-shaped, and the flowers lack true petals.
- The fruit is a small, round, berry-like drupe, initially green, turning red when mature, and eventually dark purple or black.
- The fruit is smooth, indehiscent, and typically glabrous.

Leaves, Stem, and Roots:

The plant is a shrub or small tree, growing up to 2–4 meters in height.

➢ **Leaves:**

- Simple, alternate, and elliptic to ovate in shape.
- The upper surface is dark green, while the underside is pale green.
- The leaf margins are entire, and the petiole is short.

➢ **Stem:**

- Woody at the base, with smooth to slightly hairy bark.
- Young branches are often slender and slightly angular.

➢ **Roots:**

- The plant has a fibrous root system.
- In some traditional systems, the roots are used for medicinal purposes.

Characteristics:

- The flowers emit a mild fragrance that attracts pollinators.
- The plant is drought-resistant and commonly found in tropical and subtropical regions.
- It plays a significant ecological role in soil stabilization and wildlife habitat.

Chemical Constituents

The plant contains Preliminary phytochemical screening of *B. Vitis-idea* contains a variety of phytoconstituents such as alkaloids, flavonoids, carbohydrates, tannin, saponin, terpenoids, phenol, protein, steroids, and glycosides.[71]

Traditional medicinal uses

1. Bark is an astringent.
2. Research has demonstrated qualities such as antioxidant, radical scavenging, antidiabetic, anti-inflammatory, anticancer, antifungal, larvicidal, adaptogenic, antihyperglycemic, hypolipidemic, hepatoprotective, and tyrosinase-inhibiting effects.[71]

➢ **Preliminary Phytochemical Screening of Extract**

The Preliminary Phytochemical screening was performed the results are as follows:

Table No. 9: Phytochemical screening of *Breynia rhamnoides* extract

Sr. No	Phytoconstituents	Ethanol extract	Aqueous extract
1	Alkaloids	+ve	+ve
2	Glycoside	+ ve	+ ve
3	Flavonoids	+ ve	+ ve
4	Tannins	+ve	+ve
5	Terpenoids	+ve	+ve
6	Saponins	+ve	+ve
7	Phenols	+ve	+ve
8	phenolic glycosides	+ve	+ve
9	Carbohydrates	-ve	-ve
10	Iridoids	+ve	+ve

+ve indicates present -ve indicates absent

Preliminary Phytochemical Screening of ethanolic extract of *Breynia rhamnoides* shows the presence of Glycosides, Flavonoids, Tannins, Iridoids, Terpenoids, and Saponins.

➢ **Pharmacological Activities**

1) **Antidiabetic, Nephroprotective, and Cardioprotective Effects**

In a study using high fructose diet-induced diabetic C57BL/6J ob/ob mice, Breynia rhamnoides leaf extracts demonstrated:

2) **Antidiabetic Activity:** Significant, dose-dependent reduction in serum glucose levels and improved glucose tolerance.

3) **Nephroprotective Effects:** Reduction in urinary total protein levels, indicating improved renal function.

4) **Cardioprotective Features:** Decreased LDL and VLDL levels, with an increase in HDL, suggesting a favorable lipid profile.

5) **Antioxidant Activity**

Extracts from Breynia species, including Breynia rhamnoides, have shown significant dose-dependent radical scavenging activity. The antioxidant properties are attributed to their phenolic and flavonoid contents. The plant exhibits significant antioxidant properties, primarily due to the presence of flavonoids, polyphenols, and other phenolic compounds. These compounds scavenge free radicals and reduce oxidative stress, which is implicated in aging and various chronic diseases. Methanolic and ethanolic extracts have shown potent DPPH and ABTS radical scavenging activity in in vitro assays.

6) **Larvicidal Activity**

Leaf extracts of Breynia vitis-idaea, a species closely related to Breynia rhamnoides, exhibited larvicidal properties against mosquito vectors such as Aedes aegypti, Culex quinquefasciatus, and Anopheles stephensi. This suggests potential for natural mosquito control agents.

7) Wound Healing and Anti-inflammatory Uses

Traditional applications in India include:

Wound Healing: Bark used for treating wounds.

Anti-inflammatory: Powdered dried bark and leaves used as smoke to treat swelling of the tongue and amygdala.

Postpartum Care: Leaf juice is given to mothers after childbirth.

Treatment of Skin Conditions: Leaves used for psoriasis and scabies.

Breynia rhamnoides has demonstrated anti-inflammatory effects in both acute and chronic models. The extracts inhibit the production of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6, and also downregulate the expression of COX-2 and iNOS enzymes, which are key players in the inflammation cascade.

8) Nanoparticle Synthesis and Catalytic Activity

Breynia rhamnoides stem extract has been utilized in the green synthesis of gold and silver nanoparticles. These biogenic nanoparticles effectively catalyze the reduction of 4-nitrophenol to 4-aminophenol, highlighting their potential in environmental remediation and industrial applications.

9) Antibacterial and Antimicrobial Activity

Extracts from the plant are effective against various gram-positive and gram-negative bacteria, including Escherichia coli, Staphylococcus aureus, and Pseudomonas aeruginosa. This antibacterial effect is thought to stem from secondary metabolites such as tannins, saponins, and alkaloids, which disrupt microbial cell walls and interfere with protein synthesis.[72]

❖ Traditional and Ethnomedicinal Uses

Breynia rhamnoides has been employed in various traditional remedies:

- **Mouthwash:** Root decoction used as a mouthwash in India.
- **Toothstick:** Mature stem used as a herbal toothstick by Tamil ethnic communities.
- **Jaundice Treatment:** Leaf juice is administered for jaundice in Tamil Nadu.
- **Herpes Treatment:** Leaves used in the treatment of herpes in Coastal Karnataka.
- **Swelling Reduction:** Leaves applied to treat swelling of the legs and testis in Andhra Pradesh.
- **Uterine Fibroids:** Crushed leaves consumed with milk to treat uterine fibroids in Karnataka.
- **Skin Diseases and Boils:** Leaves used for boils, skin diseases, and bleeding by the Malayali tribe in the Eastern Ghats, India.[73]

CONCLUSION AND FUTURE PROSPECTS

Breynia rhamnoides is an emerging medicinal plant that holds immense promise as a source of pharmacologically active constituents. With a history rooted in traditional medicine and increasing validation from preliminary scientific studies, this plant has demonstrated diverse therapeutic potentials, including antioxidant, anti-inflammatory, antimicrobial, antidiabetic, hepatoprotective, and wound healing properties. The growing interest in plant-based medicines makes *Breynia rhamnoides* a relevant candidate for further research and development in the field of phytomedicine and drug discovery. Despite encouraging findings from in vitro and in vivo studies, the integration of *Breynia rhamnoides* into modern medical practice remains limited due to several scientific and regulatory gaps. First and foremost, the isolation and structural characterization of its bioactive compounds are yet to be fully explored. Although preliminary phytochemical screening has confirmed the presence of flavonoids, alkaloids, tannins, phenolic acids, and saponins, advanced techniques such as HPLC, GC-MS, NMR, and LC-MS/MS are necessary to identify, purify, and characterize specific molecules responsible for the observed pharmacological actions. Identifying lead compounds with reproducible efficacy will also enable targeted drug development and structure-activity relationship (SAR) studies. Furthermore, standardization of plant extracts is essential for ensuring reproducibility, efficacy, and safety in both research and clinical settings. Variability in phytochemical content due to differences in geographical location, harvest time, and extraction methods poses a significant challenge. Standardized formulations will provide consistency in bioactive compound concentrations, which is vital for both experimental studies and therapeutic applications. A major bottleneck in the clinical advancement of *Breynia rhamnoides* is the lack of pharmacokinetic and pharmacodynamic data. These studies are critical to understanding the absorption, distribution, metabolism, and excretion (ADME) of its active components, as well as their interactions with cellular targets and signaling pathways. Understanding these mechanisms will help clarify the therapeutic window, dosing regimen, and potential drug-herb interactions.Moreover, comprehensive clinical trials are required to validate the safety and efficacy of *Breynia rhamnoides* in human subjects. Although traditional usage and animal models provide foundational insight, clinical evidence is indispensable for its approval and use in evidence-based medicine. Toxicological profiling, including genotoxicity, reproductive toxicity, and chronic toxicity, should also be prioritized to ensure long-term safety. Given its diverse pharmacological spectrum, *Breynia rhamnoides* has the potential to contribute meaningfully to natural drug discovery and integrative medicine. Its bioactive molecules could serve as leads for the development of new therapeutic agents, either as standalone drugs or as synergistic components in polyherbal formulations. In an era where antimicrobial resistance, chronic inflammation, and metabolic disorders are on the rise, natural compounds from plants like *Breynia rhamnoides* offer a promising complementary approach to conventional therapies. In conclusion, *Breynia rhamnoides* stands at the intersection of traditional wisdom and modern science. With targeted research focusing on its phytochemistry, pharmacology, and clinical validation, this underutilized plant could soon emerge as a valuable asset in the global pharmacopeia.

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