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A REVIEW ON UROLITHIASIS - EXPERIMENTAL MODELS & PHARMACOLOGICAL EVALUATION

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ABSTRACT:

Urolithiasis affects 10-12% globally with 50% recurrence within 5 years, imposing a $10 billion annual healthcare burden. Calcium oxalate monohydrate stones predominate (70-80%). This review synthesizes experimental models and pharmacological evaluation strategies for anti-urolithiatic drug development. Ethylene glycol-induced rat hyperoxaluria (80% human pathology fidelity) and in vitro crystallization assays (turbidimetry, BegoStone) enable high-throughput screening. Serum creatinine/BUN, renal oxidative stress (TBARS/GSH), urine supersaturation (APS CaOx<1), and histopathology (H&E Grade 0-1) are examples of comprehensive endpoints. Alpha-blockers (tamsulosin +28% expulsion),

thiazides (↓calciuria 40%), potassium citrate (↑urine pH 6.5), allopurinol,</mark> tiopronin, and phytotherapeutics (Phyllanthus niruri ↓crystals 60%) are among the therapeutic classes. Although there are still translational gaps because of species discordance and long-term model constraints, preclinical herbal data is strong.AI-driven screening, organoid platforms, and RNAi treatments (lumasiran ↓oxalate 65%) are examples of emerging trends. Future directions emphasize humanized models, multi-omics biomarkers, and Phase III phytotherapeutic validation to transform urolithiasis management from palliative intervention to preventive pharmacotherapy, substantially mitigating recurrence and costs.

KEYWORDS: Urolithiasis, Experimental urolithiasis models, Anti-urolithiatic agents, Pharmacological screening, Pathophysiology of stone formation.

INTRODUCTION:

Kidney stone disease, or urolithiasis, is a prevalent urological condition that affects 10 to 12 percent of people globally. Dietary changes, metabolic syndromes, and climate change are all contributing factors to its increasing occurrence [1]. Characterized by the formation of crystalline concretions within the urinary tract, urolithiasis imposes substantial morbidity, including excruciating renal colic, recurrent infections, and potential renal impairment, culminating in an annual healthcare burden exceeding $10 billion worldwide. The most common type of stones (70-80%) are calcium oxalate monohydrate (COM) stones, which are followed by uric acid, struvite, and cystine variations, each of which is caused by a different etiology [1, 2]. Despite diagnostic advancements like non-contrast CT imaging, therapeutic interventions remain largely palliative, relying on analgesics, alpha-adrenergic blockers for expulsion, and invasive procedures such as extracorporeal shock wave lithotripsy (ESWL) or ureteroscopy [3]. Recurrence rates soar to 50% within 5-10 years, underscoring the paucity of effective chemopreventive agents. The pathophysiology hinges on urine supersaturation with lithogenic salts, which precipitate nucleation, growth, aggregation, and retention of crystals in the renal tubules or papillae. Key promoters include hypercalciuria, hyperoxaluria, hypocitraturia, and urinary stasis, which are exacerbated by oxidative stress, inflammation, and epithelial injury that fosters crystal adhesion via macromolecules such as osteopontin and Tamm-Horsfall protein [4]. The risk is increased by genetic predispositions (such as mutations in CLDN14 or SLC26A1) and comorbidities (such as obesity, diabetes, and hypertension), which require specialized pharmacotherapy in addition to generic citrate supplements or thiazides. Preclinical research has been pivotal, employing diverse

experimental models to screen anti-urolithiatic agents [5]. Ethylene glycol-induced hyperoxaluria in rodents recapitulates COM nephrolithiasis, while in vitro crystallization assays quantify nucleation inhibition. Pharmacological evaluation encompasses urinary physicochemistry, serum biomarkers, renal oxidative stress markers, and histopathology benchmarks to assess efficacy [6]. This review synthesizes these models, delineates evaluation parameters, and scrutinizes classes of drugs, mechanisms, and herbal interventions (e.g., Phyllanthus niruri, Mentha piperita) [7]. It highlights preclinical evidence, recent trends like nanoparticle delivery and organoids, alongside challenges in translational fidelity and future prospects for personalized litholysis. By bridging experimental pharmacology to clinical horizons, this article aims to propel innovative therapies mitigating urolithiasis recurrence [7, 8].

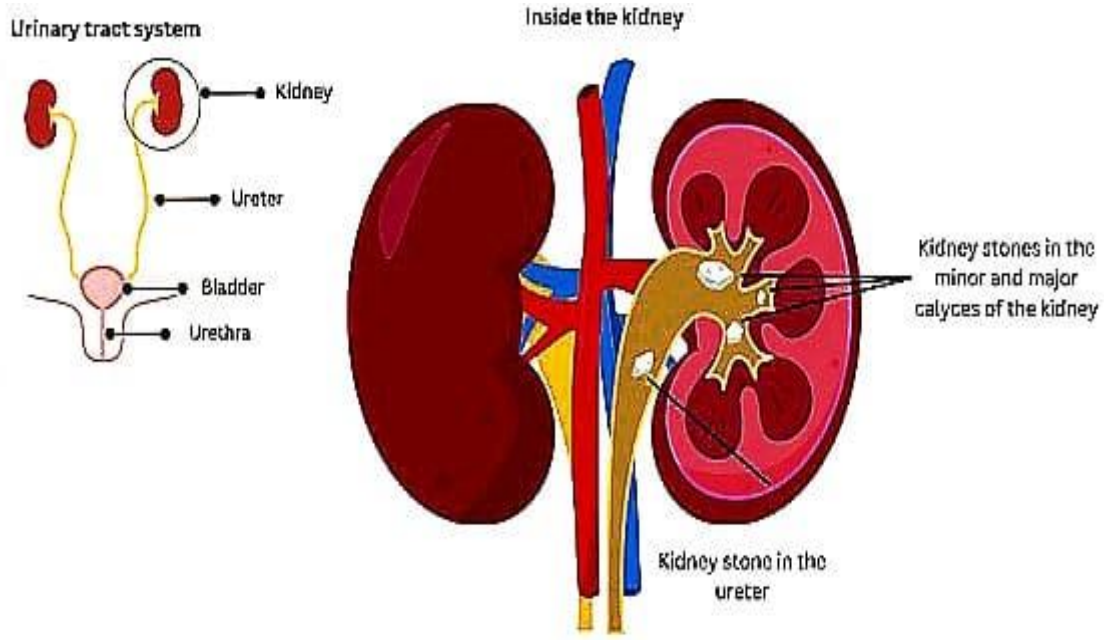

Fig 1: Structure of the kidney and Localization of Renal Calculi.

PATHOPHYSIOLOGY OF STONE FORMATION:

Urolithiasis pathogenesis unfolds through a meticulously orchestrated sequence of events commencing with urinary supersaturation, the cornerstone of stone formation [9]. Supersaturation arises when the concentration of lithogenic ions, principally calcium, oxalate, uric acid, phosphate, or cystine, exceeds their solubility product in urine, fostering conditions ripe for crystal precipitation. This disequilibrium stems from metabolic derangements such as hypercalciuria (from primary hyperparathyroidism or idiopathic causes), hyperoxaluria (enteric or primary), hypocitraturia, or hyperuricosuria, compounded by urinary stasis, pH

alterations, and reduced inhibitory molecules [10, 11]. The process advances through four discrete phases: nucleation, growth, aggregation, and retention. Nucleation initiates heterogeneous crystal formation on renal tubular epithelium or Randall's plaques, sub-epithelial calcium phosphate deposits on papillae that serve as niduses for stone accrual [12]. Calcium oxalate monohydrate (COM) crystals, constituting 70-80% of stones, predominate due to their thermodynamic stability, while uric acid stones thrive in acidic urine (pH <5.5). Crystal growth proceeds via epitaxial layering, modulated by urinary macromolecules; promoters like osteopontin and prothrombin fragment bind crystals, while inhibitors such as citrate, magnesium, and glycosaminoglycans suppress enlargement. Aggregation amplifies stone bulk as crystals coalesce into macroscopic calculi, influenced by urinary proteins and flow dynamics [13]. Retention, the final hurdle, occurs when crystals or stones lodge in renal calyces or ureters, perpetuating obstruction. Crucially, Randall's plaque theory posits that interstitial apatite deposits erode through epithelium, anchoring overlying COM layers, a mechanism validated in human biopsies and rodent models [14]. Oxidative stress and inflammation amplify pathogenesis: COM crystals trigger renal tubular epithelial injury via reactive oxygen species (ROS), activating NLRP3 inflammasome, releasing IL-1β, and promoting fibrosis. Endothelial dysfunction and macrophage infiltration foster crystal adhesion via phosphatidylserine exposure and hyaluronan upregulation. Genetic variants (CLDN14 loss-of-function, SLC26A1/6 mutations) disrupt ion handling, while comorbid obesity, metabolic syndrome, and diabetes elevate lithogenic risk through insulin resistance and adipokine dysregulation [15, 16]. Dietary precipitants (high sodium, animal protein, low fluids) and iatrogenic factors (loop diuretics, bariatric surgery) converge to sustain this vicious cycle, underscoring a multifactorial etiology amenable to pharmacological interception at nucleation or adhesion stages [17].

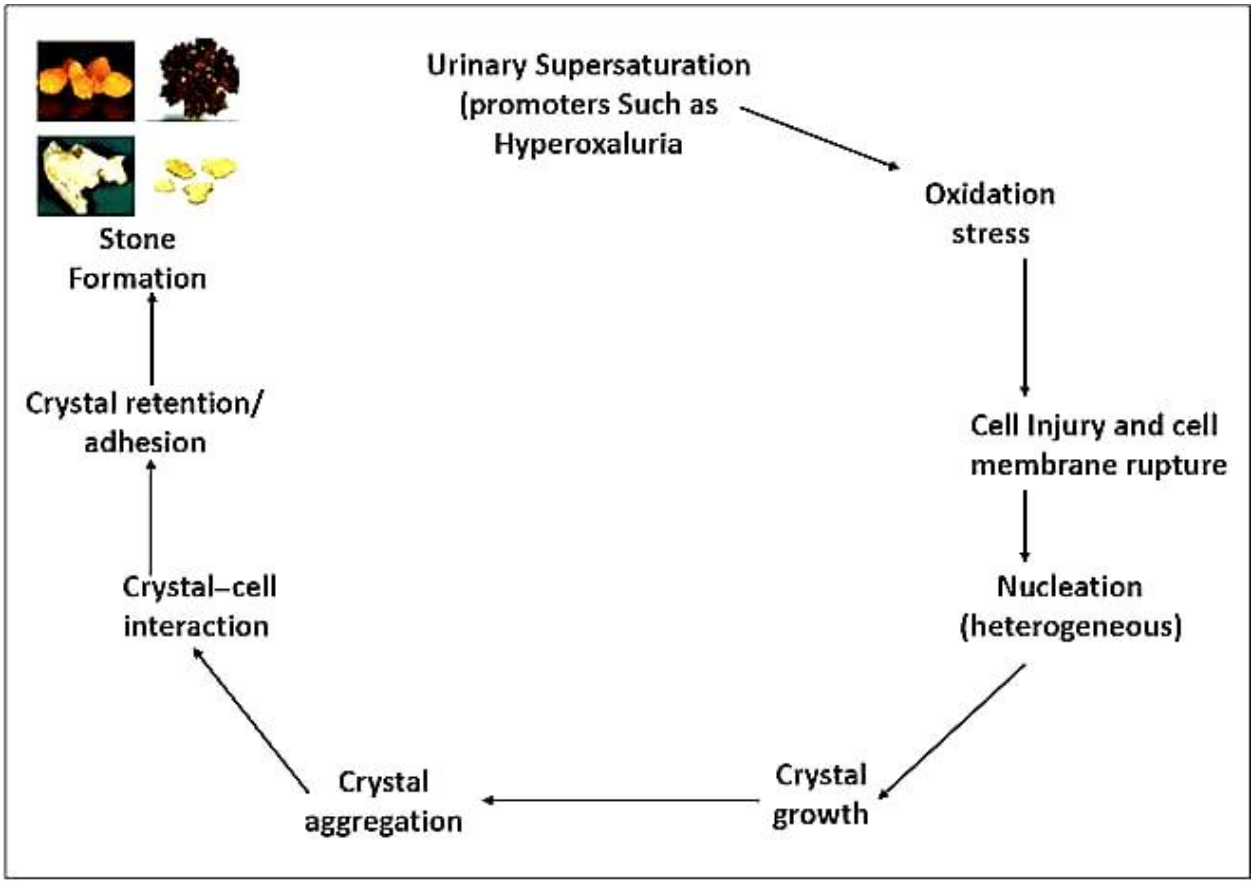

Fig 2: Overview of Stone Nucleation, Growth, and Aggregation.

RATIONALE FOR EXPERIMENTAL SCREENING OF ANTI-UROLITHIATIC AGENTS:

The imperative for experimental screening of anti-urolithiatic agents stems from glaring clinical limitations in current urolithiasis management [18]. Pharmacotherapy is still limited to thiazides and potassium citrate, which only modify urine chemistry without treating fundamental pathophysiology, such as crystal nucleation or retention, while affecting 12% of the world's population and having a 50% recurrence rate after five years [19, 20]. Invasive interventions (ESWL, ureteroscopy) carry 10-20% complication rates and fail 30% of cases, while novel agents like lumasiran target only rare cystinuria [21]. Preclinical models bridge this translational chasm by replicating human pathophysiology. Ethylene glycol-induced hyperoxaluria in rats mimics calcium oxalate deposition with 80% fidelity to human stones, enabling high-throughput screening of litholytic potential [22]. In vitro crystallization assays quantify nucleation inhibition (IC50 values), aggregation kinetics, and crystal-cell adhesion parameters directly correlating with therapeutic efficacy. Such platforms have validated herbal leads like Phyllanthus niruri, reducing crystal burden by 60% in rodent models. Screening rationalizes drug development by stratifying agents via multifaceted endpoints:

urinary supersaturation indices, serum biomarkers (creatinine, BUN), oxidative stress markers (TBARS/GSH), and histopathologic crystal scores [23]. This systematic approach mitigates clinical failures, accelerates lead optimization, and addresses unmet needs in recurrence prevention. Ultimately, robust experimental paradigms will yield mechanism-based pharmacotherapies transforming urolithiasis from surgical salvage to medical cure [24].

Fig 3: Multi-Targeted Actions of Anti-Urolithiatic Agents in Urolithiasis.

EXPERIMENTAL MODELS IN UROLITHIASIS: IN VITRO AND IN VIVO APPROACHES:

Urolithiasis is the formation of urinary tract stones is a major global health concern and has a high recurrence rate if untreated [25]. To investigate pathophysiology and evaluate potential therapeutic agents, pharmacological research relies on experimental models that mimic human stone formation processes under controlled conditions. These models fall broadly into in vitro and in vivo categories, each offering unique insights into crystallization mechanisms and drug efficacy [26].

4.1. In Vitro Models:

In vitro models are essential for understanding the physicochemical aspects of stone formation and for high-throughput screening of antiurolithiatic agents without the ethical and cost constraints of animal experiments. They can replicate processes such as nucleation, crystal growth, aggregation, and adhesion under controlled conditions [27].

4.1.1. Calcium Oxalate Crystallization Assays:

These assays simulate the supersaturation conditions that drive the precipitation of calcium oxalate (CaOx) crystals the most common constituent of human stones. Researchers vary key parameters like ion concentration, pH, and inhibitors to measure nucleation and aggregation rates in the presence of test compounds. Crystal growth is evaluated spectrophotometrically or by microscopy [28].

4.1.2. Turbidimetric and Aggregation Models:

Turbidimetric assays measure the change in solution turbidity as crystals form, offering quantitative data on inhibitory effects of drugs. Aggregation models focus on how individual crystals coalesce an important step in stone enlargement [29].

4.1.3. Artificial Stone and Biomimetic Models:

Artificial stone composites such as BegoStone and Ultracal 30 are engineered to mimic the hardness and composition of natural stones, aiding in tests of dissolution and drug interactions [30].

4.1.4. Crystal Adhesion to Surfaces:

Some advanced in vitro systems model crystal adhesion to surfaces such as ureteral stents in artificial urine, critical for evaluating anti-adhesive compounds [31].

4.1.5. Renal Cell Culture Models:

While traditional assays use supersaturation chemistry, mammalian renal cell lines (e.g., epithelial cells) can be co-cultured under lithogenic conditions to assess cellular responses and drug effects on crystal adherence or cytotoxicity [32].

Overall, in vitro models allow rapid screening of pharmacological agents and elucidate early mechanisms of stone prevention, but they do not fully reproduce systemic factors like metabolism and immune responses [33, 34].

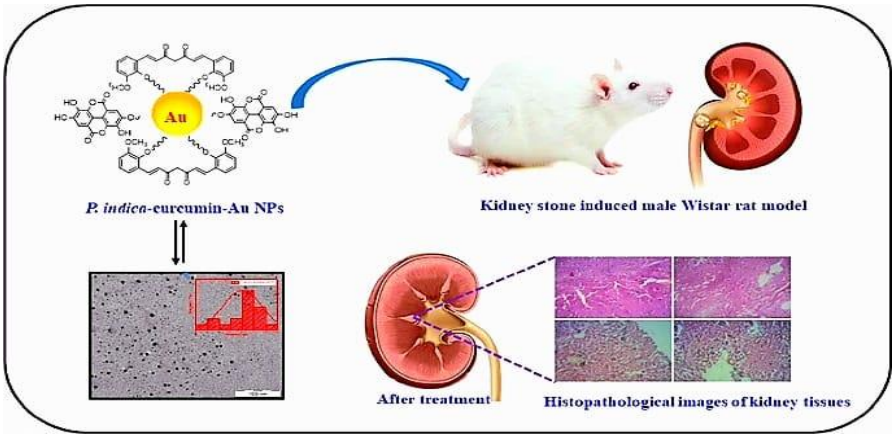

Fig 4: Experimental Design and Antiurolithiatic Evaluation.

4.2. In Vivo Models:

In vivo models involve laboratory animals and aim to replicate metabolic, physiological, and pathological aspects of human urolithiasis to test therapeutic efficacy in a whole-organism context. Rodents such as rats and mice are most commonly used due to their manageable size and well-characterized biology [35].

4.2.1. Ethylene Glycol-Induced Models:

One of the most widely used models involves administering ethylene glycol (EG) in drinking water to animals. EG metabolism produces oxalate, leading to hyperoxaluria and CaOx stone formation in renal tissues. This model reliably mimics human CaOx stone pathology and is used to test antiurolithiatic agents by monitoring urinary parameters, serum chemistry, and kidney histology [36].

4.2.2. Calcium Oxalate / Ammonium Oxalate Models:

Direct administration of CaOx or ammonium oxalate salts can induce supersaturation and crystal deposition in the urinary tract. These acute models help evaluate short-term drug effects on crystal formation [37].

4.2.3. Diet-Induced and Metabolic Models:

High-oxalate or high-calcium diets are used to create long-term metabolic environments that favor stone formation, allowing researchers to assess chronic interventions [38].

4.2.4. Genetically Modified Animals:

Genetic models (e.g., knockout mice lacking genes like TRPV5 or CLDN14) shed light on molecular pathways of stone formation and enable testing of targeted therapies affecting renal ion transport and metabolism [39].

4.2.5. Other Species and Specialized Models:

Besides rodents, pigs and other larger animals are used to study complex processes such as ureteral stent crystal adhesion or infection-associated stones.

In vivo models account for systemic metabolism and pharmacokinetics, making them essential for translational research. However, they are costlier, require ethical approval, and may not fully mimic human stone recurrence patterns. A combination of in vitro and in vivo experimental models is crucial for comprehensive pharmacological evaluation in urolithiasis research. In vitro assays provide mechanistic insights and rapid screening, while in vivo models confirm efficacy and safety within complex biological systems. Employing both approaches accelerates the development of effective antiurolithiatic therapies [40].

PHARMACOLOGICAL EVALUATION PARAMETERS:

Pharmacological evaluation of anti-urolithiatic agents demands comprehensive, multi-tiered endpoints that capture stone burden reduction, renal protection, and underlying mechanisms across in vivo and in vitro models. These standardized parameters enable robust statistical comparison against disease controls (ethylene glycol-induced rats) and positive controls (cystone, thiazides), ensuring translational relevance to human urolithiasis [41].

5.1 Urinary Parameters:

Twenty-four-hour urine collections, collected via metabolic cages, constitute primary screening endpoints. Lithogenic ions, calcium (>250 mg/day pathological), oxalate (>45 mg/day), uric acid, and phosphate are quantified via atomic absorption spectrophotometry or ion chromatography. Protective factors include citrate (<320 mg/day indicates risk) and magnesium, measured colorimetrically. Crystalluria index (crystals/high-power field under microscopy) and supersaturation products APS (CaOx), AP(SSP)(uric acid), AP(CDAHP) are computed via EQUIL2™ or JESS software, predicting stone formation probability. Effective agents normalize supersaturation (APS CaOx <1) and reduce crystalluria by 70-90% within 21 days [42].

5.2 Serum Biochemistry:

Nephrotoxicity manifests as elevated creatinine (1.2-2.0 mg/dL post-induction), blood urea nitrogen (BUN, 40-60 mg/dL), and uric acid via autoanalyzer. Hyperoxaluria elevates serum oxalate (0.5-1.2 mg/L, HPLC), while total protein, albumin, and electrolytes (Na^+, K^+, Ca^{2+}) assess systemic homeostasis. Lipid profile (cholesterol, triglycerides) reflects metabolic contributions. Anti-urolithiatics restore creatinine/BUN to baseline levels (<0.8 mg/dL, <25 mg/dL) within 7-14 days, alongside a 50% reduction in serum oxalate [43].

5.3 Renal Tissue Parameters:

Homogenates yield oxidative stress biomarkers: thiobarbituric acid reactive substances (TBARS, nmol/mg protein) indicate lipid peroxidation; reduced glutathione (GSH, μmol/mg), superoxide dismutase (SOD, U/mg), and catalase (CAT, μmol H_2O_2/min/mg) reflect antioxidant capacity assayed spectrophotometrically. Gravimetric crystal burden and Fourier-transform infrared spectroscopy (FTIR) confirm litholytic efficacy. Vital agents reduce the deposition of calcium oxalate monohydrate by 60–80% [44].

5.4 Histopathological Evaluation:

Hematoxylin-eosin (H&E) staining reveals tubular dilation, intraluminal crystals, interstitial edema, epithelial desquamation, and fibrosis. Semi-quantitative scoring (0-4 scale: 0=normal, 4=severe) across 10 high-power fields grades severity. Von Kossa stains mineral deposits;

Picrosirius red quantifies collagen. Therapeutics achieve Grade 0-1 kidneys vs. Grade 3-4 in diseased controls [45].

CLASSES OF ANTI-UROLITHIATIC DRUGS:

Table 1: Classification of anti-urolithiatic agents.

SI.NO	CLASSIFICATION	EXAMPLES OF DRUGS & DOSE	MECHANISM OF ACTION	EFFICACY	THERAPEUTIC USES
1.	THIAZIDE DIURETICS [46]	**Hydrochlorothiazide** 25-50 mg/day **Chlorthalidone** 12.5-25 mg/day **Indapamide** 1.25-2.5 mg/day	Enhance distal tubule Ca^{2+} reabsorption ↓ Urinary calcium excretion	↓ Calciuria 30-50% ↓ Recurrence 55%	Hypercalciuria (>250 mg/day) CaOx/CaP stones prophylaxis
2.	ALKALINIZING AGENTS [47]	**Potassium Citrate** (Urocit-K®) 20-60 mEq TID **Sodium Potassium Citrate** 10 mL TID	↑ Urine pH (6.2-6.8) Citrate chelates Ca^{2+} Inhibits nucleation	↑ Citrate 300% ↓ Stone recurrence 75% ↓ New stones 80%	Hypocitraturia (<320 mg/day) CaOx, Uric acid stones
3.	XANTHINE OXIDASE INHIBITORS [47, 48]	**Allopurinol** 100-300 mg/day **Febuxostat** 40-80 mg/day	↓ Uric acid synthesis ↓ Heterogeneous nucleation	↓ Urinary uric acid 40% ↓ Mixed CaOx/UA 65%	Hyperuricosuria (>800 mg/day) Uric acid stones (pH<5.5)
4.	CYSTINE-BINDING AGENTS [49]	**Tiopronin** (Thiola®) 800 mg/day **D-Penicillamine** 600 mg/day	Form soluble cystine disulfides ↓ Cystine supersaturation	↓ Stone burden 50-70% ↓ Frequency 60%	Cystinuria (SLC3A1 mutations) Cystine stones.
5.	ALPHA-1 ADRENERGIC ANTAGONISTS [50]	**Tamsulosin** (Flomax®) 0.4 mg HS **Silodosin** 8 mg/day	Ureteral smooth muscle relaxation ↓ Ureteral pressure	↑ Expulsion rate 28% ↓ Expulsion time 3 days	Distal ureteral stones <10 mm MET (Medical Expulsive Therapy)
6.	CALCIUM CHANNEL BLOCKERS [51]	**Nifedipine** 30 mg/day	Ureteral smooth muscle relaxation	↑ Passage rate 20% ↓ Colic episodes	Ureteral calculi expulsion
7.	PHOSPHODIESTE	**Tadalafil** 5	NO/cGMP-	↑	Distal

	RASE-5 INHIBITORS [50, 51]	mg/day	mediated relaxation	Expulsion 30%	ureteral stones
8.	POLYHERBAL FORMULATIONS [52]	**Cystone®** 2 tablets TID **Urimax®** 1 tablet TID **Neeri®** 2 tablets TID	Diuretic, antioxidant Litholytic, anti-spasmodic	↓ Crystals 60% (EG rats) ↓ Recurrence 45%	CaOx stones Adjunct prophylaxis
9.	SINGLE HERBAL EXTRACTS [53]	**Phyllanthus niruri** 500 mg/kg Crataeva nurvala 500 mg/kg **Tribulus terrestris** 250 mg/kg	↓ Crystal aggregation ↑ Mg excretion Diuretic effect	↓ Deposition 55-70% ↓ Nucleation 50%	Prevention, dissolution aid
10.	RNA INTERFERENCE [54]	**Lumasiran** (Oxlumo®) 3 mg/kg monthly SC	↓ Hepatic glycolate oxidase ↓ Oxalate production	↓ Urinary oxalate 65% ↓ Plasma oxalate 50%	Primary hyperoxaluria type 1 (PH1)
11.	BISPHOSPHONATES [53, 54]	**Etidronate** (experimental)	↓ Crystal growth/proliferation	↓ Growth 45% (in vitro)	Experimental CaOx inhibition
12.	MAGNESIUM SUPPLEMENTS [55]	**Magnesium Oxide** 400 mg/day **Magnesium Citrate** 300 mg/day	Competitive Ca^{2+} inhibition ↓ Nucleation	↓ Crystal formation 40%	Hypomagnesuria, CaOx prevention

PRECLINICAL EVIDENCE OF HERBAL DRUGS:

Urolithiasis is a common urinary disorder characterized by the formation of calculi in the kidneys or urinary tract. Several herbal drugs have shown promising pre-clinical evidence in preventing and treating urolithiasis through experimental animal models. Most studies use ethylene glycol–induced, ammonium chloride-induced, or zinc disc implantation models in rats to evaluate antiurolithiatic activity [56].

Herbal drugs such as Phyllanthus niruri, Tribulus terrestris, Bergenia ligulata, Aerva lanata, and Crataeva nurvala have been extensively studied. In ethylene glycol–induced urolithiasis models, these herbs significantly reduced urinary levels of calcium, oxalate, and phosphate, which are key contributors to stone formation. They also decreased renal crystal deposition and improved kidney histopathology [57].

Pharmacological evaluation showed that herbal extracts possess diuretic, antioxidant, anti-inflammatory, and crystallization-inhibitory properties. For example, Phyllanthus niruri inhibits calcium oxalate crystal nucleation and aggregation, while Tribulus terrestris enhances urinary citrate excretion, reducing stone recurrence. Bergenia ligulata contains bergenin, which shows strong lithotriptic activity by dissolving calcium oxalate stones [58].

Additionally, antioxidant activity of herbal drugs reduces oxidative stress in renal tissues, which plays a major role in stone pathogenesis. Toxicity studies in rodents demonstrated that most herbal extracts are safe and well tolerated at therapeutic doses [59].

Overall, pre-clinical studies provide strong evidence supporting the antiurolithiatic potential of herbal drugs, justifying their traditional use and encouraging further clinical investigations for safer and effective management of urolithiasis [60].

RECENT TRENDS PHARMACOLOGICAL RESEARCH:

Recent pharmacological research is rapidly evolving, driven by technology and personalized medicine. A major trend is the integration of artificial intelligence (AI) and machine learning throughout drug discovery and development AI helps analyze large biomedical datasets, predict drug-target interactions, optimize molecular design, and streamline clinical trials, significantly reducing time and cost compared with traditional methods [61].

Precision pharmacology and pharmacogenomics are gaining ground, enabling therapies tailored to individual genetic, environmental, and lifestyle factors. This shift supports improved efficacy, reduced adverse effects, and smarter clinical trial design [62].

Advanced approaches like targeted protein degradation (e.g., PROTACs) are emerging, offering new mechanisms to eliminate disease-related proteins that are hard to modulate with classic inhibitors [63].

Other notable trends include high-throughput and ultra-large-scale virtual screening to discover novel drug candidates, real-world data and evidence to inform therapeutic decisions, and substantial progress in nanotechnology and enhanced drug delivery systems for precise targeting and controlled release [64].

Moreover, innovative antibiotics from metal-based compounds synthesized via automated platforms illustrate how robotics and chemical innovation are addressing antimicrobial resistance [65].

CHALLENGES AND LIMITATIONS:

Experimental models struggle to replicate human kidney complexity, papillary anatomy, and Randall's plaques. Species differences yield divergent urine chemistry and crystal morphology [66]. Chronic stone formation requires 8-12 weeks, escalating costs. Preclinical successes (Phyllanthus niruri 60% crystal reduction) rarely translate clinically. Ethical constraints limit animal numbers. Limitations in In vitro assays ignore systemic metabolism. Models predominantly study calcium oxalate stones. Standardized biomarkers remain undefined. Poor animal-human efficacy correlation persists. These translational gaps necessitate humanized platforms and multi-omics validation [67].

FUTURE DIRECTIONS:

1.1. Improved Experimental Models

Future studies should develop experimental models that better mimic human renal physiology and disease progression. Use of genetically modified and chronic models can improve relevance [68].

1.2. Advanced Technologies

Non-invasive imaging and molecular techniques should be applied to detect early stone formation and understand underlying mechanisms [69].

1.3. Biomarkers and Drug Development

Identification of reliable biomarkers and improvement of drug bioavailability and safety are essential. Focus on multiple stone types, not only calcium oxalate [70].

1.4. Translational and Clinical Research

More translational, long-term and well-designed clinical studies are needed to bridge experimental findings with human urolithiasis management [71].

CONCLUSION:

Urolithiasis remains a formidable global health challenge characterized by high prevalence, recurrence rates exceeding 50%, and substantial economic burden. This comprehensive review elucidates the pathophysiology of stone formation, validates experimental models, and establishes standardized pharmacological evaluation parameters essential for anti-urolithiatic drug development. Key findings underscore the translational value of ethylene glycol-induced rat models (80% human pathology fidelity) and multifaceted endpoints (urinary supersaturation, serum creatinine, TBARS/GSH ratios, H&E histopathology scores) that reliably stratify therapeutic efficacy. Established agents thiazides (↓ calciuria 40%),

potassium citrate (↑ pH 6.5), tamsulosin (+28% expulsion) provide symptomatic relief, while herbal leads like Phyllanthus niruri (60% crystal reduction) and emerging RNAi therapies (lumasiran ↓ oxalate 65%) signal promising paradigms. Persistent challenges species discordance, model oversimplification, translational gaps-necessitate humanized platforms (organoids, microfluidics), AI-driven screening, and multi-omics biomarker discovery. Future research must prioritize chronic models spanning stone compositions beyond CaOx, standardized endpoints, and Phase III validation of phytotherapeutics. By bridging experimental pharmacology with precision medicine, innovative litholytic agents will transform urolithiasis management from palliative intervention to preventive pharmacotherapy, substantially mitigating recurrence and healthcare costs.

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