

REVIEW ARTICLE

## NATURAL PRODUCT-BASED POLYHERBAL FORMULATIONS AS NOVEL ANTI-UROLITHIATIC AGENTS: CURRENT PERSPECTIVES, MECHANISTIC INSIGHTS AND FUTURE THERAPEUTIC OPPORTUNITIES

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**ABSTRACT:** Urolithiasis is a common urinary tract disorder affecting a large proportion of the global population and is characterized by a high rate of recurrence. The development of kidney stones is associated with several factors, including dietary habits, metabolic abnormalities, oxidative stress and urinary tract infections. Although surgical and pharmacological interventions are widely used for stone management, their long-term application is often limited by adverse effects, high treatment cost and the risk of stone reformation. In recent years, natural product-based polyherbal formulations have gained considerable attention as potential therapeutic alternatives due to their safety, affordability and multi-target pharmacological actions. These formulations combine different medicinal plants to produce synergistic effects that may inhibit crystal formation, enhance urine flow and provide renal protection. The present review summarizes current research on the preparation, phytochemical characterization and biological evaluation of polyherbal formulations with reported anti-urolithiatic activity. Experimental approaches used to assess crystal inhibition, antioxidant potential and diuretic effects are also discussed. In addition, challenges related to standardization, safety assessment and clinical validation of herbal combinations are highlighted. Overall, polyherbal formulations derived from natural products may offer promising opportunities for the development of effective and economical therapeutic strategies for the prevention and management of urolithiasis.

**Keywords:** Urolithiasis, Polyherbal formulation, Natural products, Anti-urolithiatic activity, Phytochemical screening, Pharmacological evaluation

## I. INTRODUCTION

Urolithiasis is a common urinary tract disease, which consists of the appearance of stones in the kidney, ureter or bladder. The common occurrence of this disease has been on the rise in recent years as a result of the alteration in dietary habits, a sedentary life and climatic conditions. It is believed to be a recurrent disease with the potential of severely impacting the quality of life of the affected patients [1]. The formation of the stones is a complicated physicochemical process that starts with the urine supersaturation, then it moves on to the crystal growth and aggregation. In the end, the events cause the retention of the crystals in the renal tissues and the formation of calculi. This process is known to be caused by a number of factors including metabolic disruptions, oxidative stress, low urine volume, urinary tract infections and so on. Figure 1 demonstrates the overall process that occurs in the formation of kidney stones and the potential points of therapeutic intervention [2].

Another major mode of treatment of urolithiasis is through drug therapy, lithotripsy and surgery. Despite the usefulness of these approaches in the removal of stones, they are linked to high cost of treatment, complications, and recurrent rate. There could also be some negative effects of using some such synthetic drugs in the long term. Thus, the necessity to find

safer and cheaper ways of preventing and treating this disorder increases [4].

The traditional use of medicinal plants in management of urinary diseases has been practiced in most regions across the world. It is stated that plant-based remedies exhibit the anti-inflammatory, diuretic, antioxidant, and crystal inhibitory effects which can be used to diminish the occurrence of stones [5]. Polyherbal formulations have gained popularity in the natural product research in recent years. Combined use of several herbs is thought to increase treatment efficacy by increasing the effect of the synergistic interaction and expanded pharmacological action. These formulations can work at various phases in the development of stones and offer enhanced renal cover than single herbs treatment [6].

Considering these, natural product-based polyherbal formulations have gained scientific validation as a significant field of research in view. Their background in terms of preparation procedure, phytochemical structure and bioactivity could be evaluated in order to justify their possible application in the management of urolithiasis. Therefore, the objective of the current review is to summarize and critically comment on the existing evidence on polyherbal formulations that have anti-urolithiatic properties, the mechanism of action and future therapeutic opportunities [7].

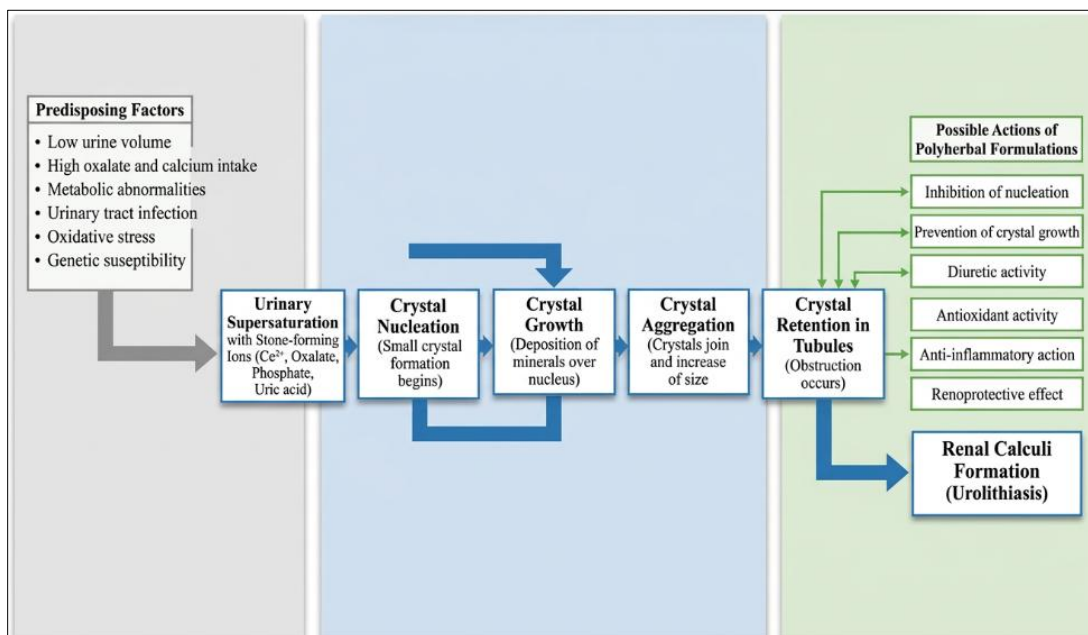


Figure 1: Pathogenesis of kidney stone formation and possible sites of herbal intervention [3]

## 2. Natural Products in the Management of Urolithiasis

### 2.1. Historical background and traditional use

Medicinal plants are traditionally used in the treatment of urinary disorders and kidney stone disease is one of them. Conventional medicine like Ayurveda, Unani and traditional Chinese medicine explain various herbal treatment which they think can induce urine flow and dissolve or prevent the development of calculi. These medicines were usually used in

decoctions, in form of powder or extracts of fresh plants [8]. The therapies that were used empirically had been subject to a long-term observation of their positive effects in alleviating symptoms like pain, burning micturition and obstruction of the urine. Has pharmacological studies have improved, most of these plants, which are traditionally used, have become the subject of scientific interest due to their possible anti-urolithiatic effects [9].

Table 1: Medicinal plants reported for anti-urolithiatic activity [15]

Plant name	Family	Part used	Major phytochemicals	Reported activity
<i>Boerhaavia diffusa</i>	Nyctaginaceae	Root / whole plant	Alkaloids, flavonoids	Diuretic, crystal inhibition
<i>Tribulus terrestris</i>	Zygophyllaceae	Fruit	Steroidal saponins	Anti-urolithiatic, urinary tonic
<i>Crataeva nurvala</i>	Capparaceae	Bark	Triterpenoids, saponins	Lithotriptic activity
<i>Aerva lanata</i>	Amaranthaceae	Whole plant	Flavonoids, tannins	Crystal growth inhibition
<i>Phyllanthus niruri</i>	Phyllanthaceae	Whole plant	Lignans, phenolics	Anti-aggregation effect
<i>Bergenia ligulata</i>	Saxifragaceae	Rhizome	Bergenin, catechins	Stone dissolution potential
<i>Herniaria hirsuta</i>	Caryophyllaceae	Whole plant	Saponins, coumarins	Anti-crystallization
<i>Dolichos biflorus</i>	Fabaceae	Seed	Proteins, flavonoids	Reduction of stone deposition
<i>Moringa oleifera</i>	Moringaceae	Leaf	Polyphenols, vitamins	Antioxidant, nephroprotective
<i>Raphanus sativus</i>	Brassicaceae	Root	Glucosinolates	Diuretic effect
<i>Ammi visnaga</i>	Apiaceae	Fruit	Khellin, visnagin	Smooth muscle relaxant
<i>Asparagus racemosus</i>	Asparagaceae	Root	Steroidal saponins	Diuretic and protective role
<i>Nigella sativa</i>	Ranunculaceae	Seed	Thymoquinone	Antioxidant, anti-inflammatory
<i>Terminalia arjuna</i>	Combretaceae	Bark	Tannins, triterpenoids	Renoprotective activity
<i>Orthosiphon stamineus</i>	Lamiaceae	Leaf	Flavonoids, terpenoids	Increased urinary output
<i>Zea mays</i> (corn silk)	Poaceae	Stigma	Flavonoids, mucilage	Diuretic action
<i>Cynodon dactylon</i>	Poaceae	Whole plant	Alkaloids, glycosides	Anti-inflammatory, diuretic
<i>Sesbania grandiflora</i>	Fabaceae	Leaf / flower	Saponins, phenolics	Crystal inhibition
<i>Camellia sinensis</i>	Theaceae	Leaf	Catechins, polyphenols	Antioxidant, anti-urolithiatic potential
<i>Urtica dioica</i>	Urticaceae	Leaf / root	Sterols, flavonoids	Diuretic, urinary cleansing

### 2.2. Common medicinal plants with reported anti-urolithiatic activity

Within recent years, a number of medicinal plants have been studied widely in terms of their anti-urolithiatic properties. The common herbs used in the traditional medicinal practice include *Boerhaavia diffusa*, *Tribulus terrestris* and *Crataeva nurvala* known to have the diuretics and lithotryptics. Equally,

other plants have been shown to have considerable potential in preventing crystal growth and aggregation such as *Aerva lanata*, *Phyllanthus niruri* and *Bergenia ligulate* [10].

Other species such as *Herniaria hirsuta*, *Dolichos biflorus* as well as *Orthosiphon stamineus* are reported to enhance urinary secretions and eliminate stone deposits. Moreover, it is possible that the antioxidant-rich plants like *Moringa oleifera*,

*Nigella sativa* and *Camellia sinensis* would play an important role in protecting the kidney because of their lessening of oxidative stress damage to the tissues. Pharmacological evidence has also confirmed the therapeutic usefulness of some other medicinal plants that were traditionally used in urinary disorders. Table 1 is a concise overview of a list of such plants with their phytochemical components and reported activities [11].

### 2.3. Role of phytoconstituents in stone prevention

Phytochemicals that are available in medicinal plants play an important role in the regulation of the mechanisms that play roles in kidney stones development. Flavonoid and saponin, alkaloids, terpenoids and phenolic acid are reported to have an influence on crystal nucleation, growth and aggregate [12]. The antioxidant formulation would potentially aid in the inhibition of oxidative stress of the epithelial cells in the kidney and consequently reduce the risk of crystal deposition. Phytochemicals are also known to raise urine, and alter urinary biochemical parameters, which are also preventive factors. These natural components are synergistic in nature, which helps in the treatment value of the interventions based on the plant in the case of urolithiasis [13].

### 2.4. Advantages of herbal therapy

Herbal treatment has a number of benefits compared to the mainstream treatment methods. Plant-based remedies are

usually regarded as being safer and less expensive especially when taken in the long-term in a recurrent condition like urolithiasis. Several active constituents can be available, which can offer synergistic pharmacological effects and expand the scope of treatment. Besides, herbal preparations can be linked to a reduction in adverse reactions in the case of proper dosages. These advantages have promoted the increased research interest in standardized herbal and polyherbal preparation of kidney stones [14].

## 3. Concept and Rationale of Polyherbal Formulation

### 3.1. Definition and scientific basis of polyherbalism

Polyherbalism is the application of two or more medicinal plants in one therapeutic formulation with the intention of producing a pharmacological effect that is superior. This principle has been extensively applied in old regimens of medicine, elaborate herbal preparations were to be made so that they would affect various pathological mechanisms at the same time [16]. Scientifically, polyherbal preparations are deemed to be rational when the components of plants have complementary mechanisms of action. The application of herbal combinations can be used in the management of urolithiasis as it can be used to regulate various phases of stone formation, such as supersaturation, crystal nucleation and injury of renal tissues [17].

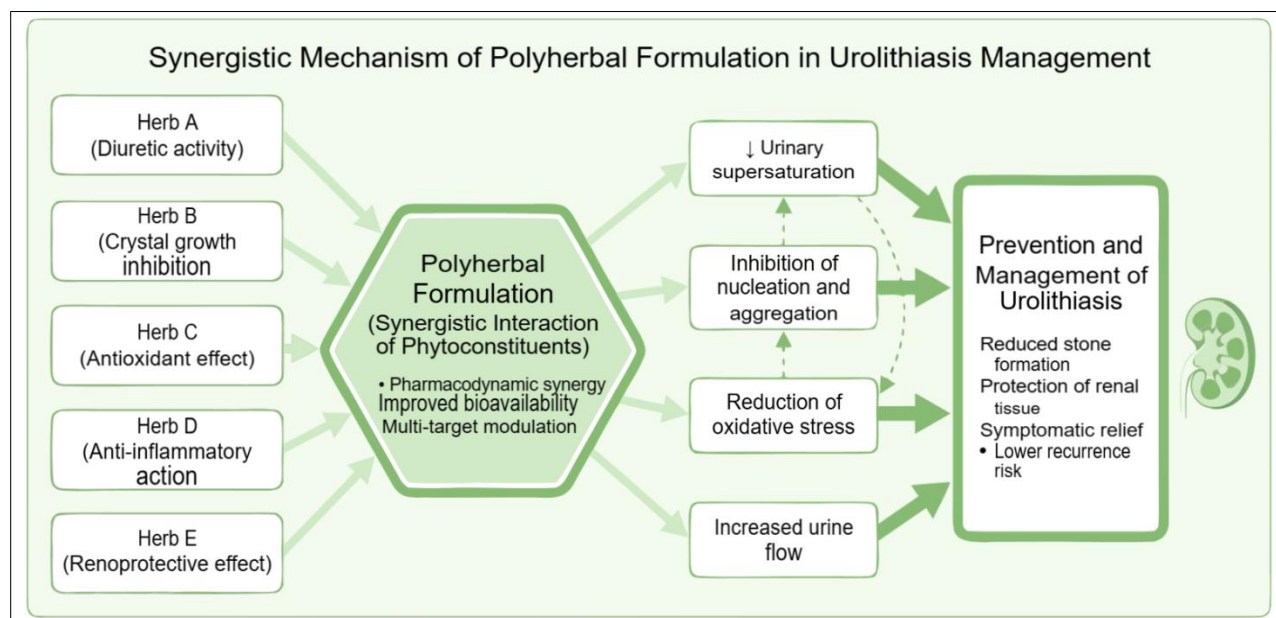


Figure 2: Schematic illustration showing synergistic pharmacological interactions of polyherbal formulations and their multi-target mechanisms involved in the prevention and management of urolithiasis

### 3.2. Synergistic and additive pharmacological effects

It is believed that the therapeutic action of polyherbal preparations is usually due to synergistic or additive effects of the phytoconstituents of polyherbal preparations. Some components in plants can boost the effects of diuretic, others can demonstrate the antioxidant, anti-inflammatory, and

crystal inhibitory effects. These effects when used in combination may result in better prevention of stone formation and enhanced protection of renal activity. Synergistic action could also improve the bioavailability of active constituents and decrease the dose of therapy. Figure 2 represents the potential multi-target effects by which polyherbal preparations would work in the urolithiasis management [18].

### 3.3. Advantages over single-herb formulations

There are various advantages of polyherbal preparations compared to single-herb therapy. The presence of a large number of bioactive compounds allows a broader coverage of therapy and can be used to enhance overall efficacy. Such kind of formulations are generally associated with reduced toxicity due to balanced pharmacological activity of individual constituents [19]. Besides, the chances of the failure of drugs and the relapse of the disease may be decreased based on herbal formulas. These properties make polyherbal techniques particularly effective in the instance of chronic and recurrent conditions such as kidney stone disease [20].

### 3.4. Challenges in formulation development

Although scientifically validated polyherbal formulations can be used therapeutically, there are some challenges in developing them. Geographical and seasonal changes in phytochemical composition have the potential to affect the consistency in the formulations. Normalization of raw materials, streamlining of extraction processes and setting of quality control parameters are needed but, in most cases, can be hard to attain [21].

Also, the existing clinical evidence and deficient regulation principles can interfere with the transformation of traditional formulations to evidence-based phytopharmaceutical products. To make sure that the safety, efficacy and further acceptance of polyherbal therapies in the management of urolithiasis, these issues need to be addressed [22].

## 4. Preparation and Standardization of Polyherbal Formulations

### 4.1 Selection of plant materials

Effective polyherbal formulation development commences with the prudent choice of appropriate medicinal plants depending on the conventional information, reported pharmacological efficacy and provision of scientific data. Plant materials have to be identified and authenticated properly to be able to guarantee formulation reliability and therapeutic consistency [23]. Identification is typically done by either macroscopic and microscopic observation,

taxonomic validation and comparison of standard herbarium specimens. Moreover, analysis of raw materials including foreign matter, moisture content and potential contamination is another way of quality and safety assurance. Choice of correct parts of the plant like roots, leaves, bark or seeds also contributes significantly to ascertain the overall efficacy of the formulation [24].

### 4.2 Extraction and processing methods

One of the most important processes in the extraction of bioactive constituents of medicinal plants is extraction. The standard techniques like maceration are common because they are simpler and also in the case of compounds that are sensitive to heat. Another technique that is frequently used is Soxhlet extraction that enables efficient recovery of phytoconstituents by continuous extraction using hot conditions [25]. Hydro-alcoholic extraction has been widely favored in herbal studies as it enables the extraction of polar and moderately non-polar compounds and consequently improves the therapeutic spectrum of the preparation. Over the past few years, green extraction methods including ultrasound-assisted and microwave-assisted have received interest to enhance the efficiency of extraction along with minimizing the amount of solvent used, and processing duration. It requires the use of proper processing and drying conditions in order to maintain the stability and activity of the plant constituents [26].

### 4.3 Formulation design

Polyherbal preparations could be prepared in different dosage forms depending on the route of administration to be used and the therapeutic need. Dried plant extracts are also used as powder mixtures commonly because of their easy preparation and conventional acceptability. The contemporary use of medication is also regarded as the preparation of pills and capsules to provide correct dosage and enhanced compliance in patients [27]. Certainly, liquid preparations, like suspensions or decoctions, are preferable in situations where a quick absorption or local urinary tract action is required. The excipients used, particle size distribution and process of blending affects the uniformity and stability of the end product [28].

**Table 2: Standardization parameters used in polyherbal formulations [31]**

<i>Parameter</i>	<i>Method</i>	<i>Significance</i>
Organoleptic properties	Visual and sensory evaluation	Preliminary quality assessment
Moisture content	Loss on drying method	Prevents microbial growth and degradation
Total ash value	Incineration method	Indicates inorganic impurities
Acid-insoluble ash	Chemical treatment and weighing	Detects silica and earthy matter
Water-soluble extractive	Cold maceration / extraction	Estimates polar constituents
Alcohol-soluble extractive	Solvent extraction method	Indicates moderately polar phytochemicals
pH determination	Digital pH meter	Ensures formulation stability
Bulk density and tapped density	Graduated cylinder method	Helps in dosage form design
Particle size analysis	Sieving method	Affects dissolution and bioavailability
Preliminary phytochemical screening	Standard chemical tests	Detects major classes of compounds
Chromatographic fingerprinting	HPTLC / HPLC	Confirms identity and consistency
Marker compound estimation	Spectrophotometry / LC methods	Quantifies bioactive constituents
Microbial load test	Plate count method	Ensures microbiological safety
Heavy metal analysis	Atomic absorption spectroscopy	Detects toxic metal contamination
Stability studies	Accelerated stability testing	Predicts shelf life of formulation

#### 4.4 Standardization and quality control

Polyherbal formulations require standardization in order to provide consistency in races, safety, and therapy. The initial data on formulation quality is given by organoleptic assessment such as colour, odour, taste and texture. Quality parameters that are routinely measured include physico-chemical parameters (pH, ash values, extractive values and moisture content). Chromatographic or spectroscopic methods of marker-based standardization are useful in detecting and determining the quantity of characteristic phytoconstituents that cause biological activity [29]. All these parameters contribute to the formulation of credible and scientifically proven herbal formulations. Table 2 has presented important quality control parameters that are often used in polyherbal research [30].

#### 5. Phytochemical Screening and Characterization

Phytochemical screening is significant to scientific assessment of polyherbal preparations that are aimed at the use as anti-urolithiatic. Determination and description of bioactive components aid in the knowledge of the therapeutic potential, quality control and supports reproducibility of pharmacological effects. The phytochemical profile of herbal combinations is generally determined by both the qualitative and quantitative methods of analysis [32].

##### Preliminary phytochemical tests

The initial phytochemical examination normally is to establish the existence of significant categories of secondary metabolites in plant extracts and preparations. Compounds that are identified by using standard chemical tests include alkaloids, flavonoids, saponins, tannins, glycosides, terpenoids and phenolic compounds.

The screening processes give the first indication of the chemical content of the formulation and aid in the choice of extraction solvents and analytical techniques to be used in the further investigation. Though being qualitative in nature, preliminary tests are handy in case of routine quality checking and evaluation of various batches of herbal preparations [33].

##### Quantitative estimation of phytoconstituents

Phytochemicals have to be quantitatively determined to find out the therapeutic relevance and standardization of the polyherbal formulations. Through spectrophotometric methods, the estimation of the total phenolic content, total flavonoid content, and the concentration of the saponin normally is done. These analyses may provide information regarding the proportionate levels of the bioactive constituents which may comprise antioxidant, diuretic and crystal inhibitory functions [34].

The quantitative analysis can also be used in monitoring the variation that occurs due to variation in the source of plants, condition of harvesting and mode of processing. Such data can be used to build markers on the quality control measures [35].

#### Advanced analytical techniques

The contemporary analysis methods have significantly aided in the characterization of phytoconstituents of herbal preparations which are complex. The accomplishment of chemical fingerprints is very common using the technique of high-performance thin-layer chromatography (HPTLC) to find out the identity and uniformity of formula. The individual compounds that have been separated could be quantified and properly separated using the high-performance liquid chromatography (HPLC) which may prove useful in the analysis of the marker compounds with standardization [36]. Hyphenated methods are liquid chromatography mass spectrometry (LC-MS) and gas chromatography mass spectrometry (GC-MS) that give detailed structural data on non-volatile and volatile components. Moreover, other spectroscopic techniques that are used in determining and purity of phytochemicals include ultraviolet visible spectroscopy, infrared spectroscopy and nuclear magnetic resonance spectroscopy. The advanced techniques are used to improve the scientific validation and acceptability of the polyherbal formulations in the anti urolithiatic studies [37].

#### 6. Biological Evaluation of Anti-urolithiatic Activity

Polyherbal formulations have to be scientifically validated through systematic biological assessment through the use of appropriate experimental models. *In-vitro* and *in-vivo* studies are usually used to examine their ability to prevent crystal formation, relieve urinary biochemical changes and prevent renal tissue damage. These are experimental studies which give pharmacological support to the herbal combinations as a potential therapeutic agent in the treatment of urolithiasis [38].

##### 6.1 *In-vitro* experimental models

Preliminary screening *in-vitro* assays are extremely common to determine the effectiveness of plant extracts and polyherbal formulations on the basis of anti-crystallization. The nucleation test is also usually conducted in order to assess how the test samples formed are capable of inhibiting the early crystallisation of calcium oxalate under controlled conditions [39]. A reduction of turbidity or the number of crystals is viewed as an indication of the presence of inhibitory activity. The crystal growth inhibition studies are carried out to establish whether herbal formulations can prevent the crystal growth by enlarging the already formed crystals, thus preventing the development of the stone [40]. Aggregation assays also are used to analyze the ability of phytoconstituents to decrease the clustering of crystals into bigger aggregates. These *in-vitro* models are comparatively easy, cheap and effective in determining potentially successful formulations that would be investigated further *in-vivo* [41].

##### 6.2 *In-vivo* animal models

The animal models play a critical role in determining the physiological testability of the therapeutic efficacy and safety of polyherbal preparations. An example of the most widely used models applied in experimental procedures is the induced

model urolithiasis induced by ethylene glycol because it induces hyperoxaluria, and deposition of potassium oxalate crystals in the renal tissues. The other notable way through which quickish stone formation can be induced in order to determine the protective effect of the herbal therapies is the sodium oxalate model [42]. Furthermore, the model of zinc discs implantation presupposes that the foreign body is implanted on the urinary bladder, which leads to the creation

of stones on the surrounded implanted material and the possibility to assess the anti-lithic activity. The effect of the polyherbal formulations on the urinary chemistry, renal and tissue morphology are learned using such experimental systems. The illustration of the usual experimental techniques of anti- urolithiastic activity biological assessment is given in Figure 3 [43].

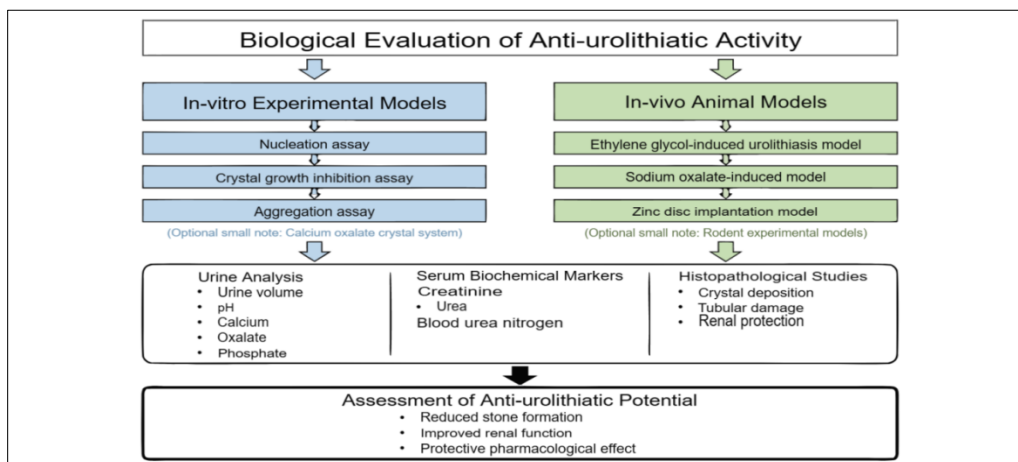


Figure 3: Schematic representation of commonly employed *in-vitro* and *in-vivo* experimental models and evaluation parameters used for assessing the anti-urolithiatic activity of polyherbal formulations

### 6.3 Evaluation parameters

The evaluation of the anti-urolithiatic activity of experimental research is done through the measurement of a number of biochemical and physiological parameters. Urine testing is conducted to identify the volume of urine, pH and levels of calcium, oxalate, phosphate and uric acid. The decrease in the concentration of the stone forming constituents and the increase in the urine output are normally considered to be favourable results [44]. Serum biochemical indicators like creatinine, urea and blood urea nitrogen are approximated to determine the state of renal functionalities. Moreover,

histopathological analysis of kidney tissues can give first-hand information about the deposition of crystals, damage to the tubules and protective impact of herbal therapy [45].

A number of studies have highlighted a high level of pharmacological effectiveness of polyherbal formulations in experimental urolithiasis models. These equations have been shown to decrease urinary supersaturation, enhance antioxidant defence systems and reduce renewable tissue harm. Table 3 gives a summarized report on reported polyherbal formulations, their composition, experimental dose, model and important pharmacological results [46].

Table 3: Reported polyherbal formulations with pharmacological outcomes [47]

Formulation composition	Dose	Model used	Key findings
<i>Boerhaavia diffusa</i> + <i>Tribulus terrestris</i>	200–400 mg/kg	Ethylene glycol model	Reduced calcium oxalate deposition and improved urine output
<i>Crataeva nurvala</i> + <i>Bergenia ligulata</i>	300 mg/kg	Sodium oxalate model	Decreased serum creatinine and renal crystal load
<i>Aerva lanata</i> + <i>Phyllanthus niruri</i>	200 mg/kg	Ethylene glycol model	Inhibition of crystal growth and antioxidant effect
<i>Dolichos biflorus</i> + <i>Tribulus terrestris</i>	400 mg/kg	Zinc disc model	Reduced stone weight and urinary oxalate level
<i>Boerhaavia diffusa</i> + <i>Crataeva nurvala</i> + <i>Bergenia ligulata</i>	250 mg/kg	Ethylene glycol model	Significant lithotriptic and renoprotective activity
<i>Moringa oleifera</i> + <i>Nigella sativa</i>	300 mg/kg	Sodium oxalate model	Improved antioxidant status and renal histology
<i>Orthosiphon stamineus</i> + <i>Phyllanthus niruri</i>	200 mg/kg	Ethylene glycol model	Increased urine volume and reduced crystal aggregation
<i>Aerva lanata</i> + <i>Dolichos biflorus</i> + <i>Crataeva nurvala</i>	400 mg/kg	Ethylene glycol model	Lowered urinary calcium and prevented tubular damage
<i>Bergenia ligulata</i> + <i>Tribulus terrestris</i>	250 mg/kg	Sodium oxalate model	Decreased crystal nucleation and improved renal markers
<i>Boerhaavia diffusa</i> + <i>Aerva lanata</i> + <i>Phyllanthus niruri</i>	300 mg/kg	Ethylene glycol model	Strong anti-urolithiatic and diuretic activity

### 7. Mechanisms of Anti-urolithiatic Action

Polyherbal formulations have their therapeutic action on various pathways of pharmacology which disrupt the main processes of kidney stone formation and progression. This is due to the presence of a wide range of phytoconstituents, which can be used at different stages of lithogenesis, and hence lead to an enhanced overall treatment outcome.

Knowledge of these mechanisms has relevance in scientific authentication and reasonable development of herbal treatment of urolithiasis [48].

#### Inhibition of crystal nucleation and aggregation

Stone formation formulation through the inhibition of crystal nucleation and aggregation is one of the major mechanisms by

which herbal formulations have this effect. Some phytochemicals can lower urinary supersaturation and mediate the binding between calcium and oxalate ions. This measure restricts the development of the early crystal nuclei and inhibits their development into bigger aggregates. Moreover, plant constituents can also modify the surface properties of crystals and therefore decrease their adhesion to renal epithelial cells. These are effects that lead to a reduction in the retention of crystals and the reduced risk of calculus formation [49].

#### **Antioxidant activity**

Oxidative stress is a major contributor of tissue damages in the kidneys and facilitates adherence of crystals in the urinary tract. Polyherbal preparations of phenolic reagents, flavonoids and other antioxidant agents aid in countering the reactive oxygen species formed in lithogenic conditions. These formulations could inhibit inflammation, cellular degeneration and crystalline deposition by eliminating oxidative stress of renal epithelial cells. An effective stimulation of endogenous antioxidant defence mechanisms is thus deemed a significant avenue of anti-urolithiatic therapy [50].

#### **Anti-inflammatory effects**

Inflammatory reactions related to tissue irritation as a result of crystals can contribute to aggravating the damage of the kidneys, as well as provoke the formation of stones. Most of the medicinal plants that are part of polyherbal preparations have anti-inflammatory effects, which reduce the discharge of pro-inflammatory mediators. Inhibition of inflammatory mechanisms can be helpful in reducing edema, enhancing renal microcirculation and preventing additional crystals. This protective mechanism helps in sustaining normal renal functioning in the state of lithogenic stress [51].

#### **Diuretic action**

The use of high volume of urine is also commonly referred to as a preventive measure to the development of kidney stones. The herbal preparations that act as diuretics aid in diluting out the urine to loosen tiny crystals that escape before combining into big calculus. The uterethral flow also aids in reducing the level of the stones that constitute ions such as calcium, oxalate and uric acid. Diuretic effect is, therefore, involved in prevention and management of urolithiasis [52].

#### **Renoprotective mechanisms**

Polyherbal preparations may also have a direct protective effect on the renal tissues, by stabilizing cell membranes and improving functional integrity of renal cells. Certain phytoconstituents are reported to control biochemical measures of renal performance and help in the repair of damaged tubular endothelium. Inhibition of urolithiastic ability of herbal combinations is further enhanced by decrease on crystal induced cytotoxicity and general health of kidneys. The importance of these renoprotective effects is to decrease

the incidence of the disease and improve the long-term therapeutic outcomes [53].

### **8. Safety, Toxicity and Clinical Evidence**

The safety and toxicity are key elements that must be evaluated during the development of polyherbal formulations that are to be used to manage urolithiasis. Despite the common view of herbal medicines as safe, systematic evaluation of the sciences is required to be able to ascertain their appropriateness in the therapeutic practice. All these studies on toxicology, interaction and any clinical or traditional evidence available are all involved in eventually validating herbal interventions [54].

#### **Acute and sub-chronic toxicity studies**

The acute toxicity studies are undertaken in an effort to identify the safe dose-range as well as the potential adverse effects of the polyherbal formulations after the administration of a single dose. These researches give initial data on behavioural changes, mortality and general physiological responses in the experimental animals [55]. Sub-chronic toxicity studies entail the administration of formulations repeatedly over a long period of time, typically a couple of weeks to test the effects on body weight, organ structure and biochemical values. The analysis of the major body organs like the liver and the kidney is made through histopathology to determine possible changes in the tissues. Results of such studies are significant in setting safety margins of therapeutic agents and choosing a level of dose to be used in pharmacological studies [56].

#### **Herb–drug interaction considerations**

Polyherbal preparations contain a number of bioactive ingredients, which may interact with other conventional drugs currently used. The interactions can result in an impact on drug metabolism, absorption or pharmacodynamic response. Certain phytochemicals are also reported to be having an impact on the activity of hepatic enzymes or renin patterns of excretions, which may result in the efficacy or safety of conventional treatments utilized in the treatment of urolithiasis [57]. Therefore, it is necessary to consider the herb-drug interaction in the appropriate way, particularly in the patients who are continually undergoing the pharmacological treatment. Science documentation and observation make it safe to integrate such interactions into clinical practice [58].

#### **Available clinical or traditional evidence**

The traditional medicinal books provide important details on the long term use of herbal medicine as a remedy to urinary diseases. A number of herbal products and polyherbal preparations in folk medicine have been used in the treatment of various symptoms like dysuria, flank pain and urinary obstruction [59]. Similar limited clinical studies as well as observational reports have also found possible advantages in some herbal combinations in the reduction of stone recurrence

as well as in the amelioration of urinary parameters in recent years. Nonetheless, randomized clinical trials are poorly designed. There is a need to generate solid clinical evidence by standardized formulations and controlled study design in order to enhance the therapeutic plausibility and broad acceptance of polyherbal ways of treating urolithiasis [60].

### 9. Challenges and Research Gaps

Despite the growing scientific interest in the use of polyherbal preparations as an alternative of tackling urolithiasis, a variety of limitations still inhibit the wider use and clinical implementation of the option. The irregularity of the phytochemical composition of medicinal plants depending on the geographical location, seasonal fluctuation, habits in growing and harvesting environments is one of the greatest issues. Such difference can influence the activity and the efficacy of herbal preparations [61]. Lack of good standardization of raw materials and finished products has also been observed in majority of studies and it makes it difficult to compare pharmacological outcomes of the products [62].

Standardized methods of extraction and formulation are the second important limitation to be considered critical. These differences in the solvent used, time and/or conditions in which the extraction is done can potentially result in a difference in concentration of bioactive constituents. In addition, quality supervision and regulatory acceptance is often compromised through the absence of clear marker compounds and accepted analysis approaches. The majority of the experimental researches are restricted to the early in-vitro studies or intermediate animal studies, but not long-term safety review, and pharmacokinetic profiling studies [63].

The clinical evidence of the effectiveness of polyherbal preparations in urolithiasis is also lacking. The enormous majority of the reported ones are based on the traditional usage or on the small scale observation studies. Standardized formulations and objective outcome measures are needed in not designed randomized clinical trials. Further, potential herb-drug interactions and variation in patient response are supposed to be studied in a systematic way [64]. The multidisciplinary approach towards addressing these gaps in research which will involve pharmacognosy, phytochemistry and pharmacology and clinical sciences will be critical towards the successful development of evidence-based herbal therapies [65].

### 10. Future Perspectives

The further studies of natural product-based polyherbal preparations should be oriented to formulation of scientifically standardized and clinically validated therapeutic products to urolithiasis. Modern analytical methods can be used to aid in the quality, stability and reproducibility of herbal products by application of modern extractions methods and advanced technologies. New delivery methods like nanotechnology-based drug delivery systems and new developmental strategies of the formulations can increase bioavailability and specific renal activity of phytoconstituents [66].

The systems biology and network pharmacology tools can be integrated to gain more understanding of the multi-target mechanisms of polyherbal formulations. These methods can help to discover interactions between phytochemicals that are synergetic and forecast their therapeutic effect. Moreover, the efficacy and safety and optimum dose regimens need to be determined in large-scale clinical trials among various patient groups [67]. The partnership between traditional medicine practitioners and pharmaceutical clinicians and scientists can also play a larger role in ensuring the translation of herbs knowledge into evidence-based healthcare solutions.

It is anticipated that further studies in the area would help to create safe, affordable and readily available treatment of kidney stone disease prevention and treatment [68].

### 11. Conclusion

Urolithiasis is a health issue as its prevalence is growing, repetitive and carries complications that impact on renal functioning and quality of life. Even though modern medical and surgical procedures prove efficient in the process of the stones removal, their shortcomings, such as negative outcomes and high recurrence rates, indicate the necessity of less harmful and more sustainable methods of therapy. In this regard, polyherbal formulations that are based on natural products have come out as credible prospects in preventing and managing kidney stone disease.

The current paper has compiled the existing knowledge available on the preparation, phytochemical profiling, and biological testing of polyherbal preparations that have anti-urolithiatic properties. Adjustable experimental data suggests that herbal blends can have a therapeutic effect in many ways, including crystal formation prevention, antioxidant and anti-inflammatory activities, urine output increase and renal tissue protection. Such multi-target pharmacological characteristics are behind the scientific conceptualization of the application of polyherbal approaches in treating lithiasis.

Nevertheless, there are issues of standardization, quality control and little clinical validation that should be tackled. It will be necessary to conduct future research studies that lay emphasis on identification of active phytoconstituents, formulation strategies that can be reproducible and implementation of well-designed clinical studies to ascertain the therapeutic credibility of these herbal interventions. On the whole, polyherbal preparations produced on the basis of natural products have a significant potential to form the successful, economical and patient-friendly anti-urolithiatic agents, should systematic scientific validation and adherence to regulatory requirements be laid.

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