Inventum Biologicum: *An International Journal of Biological Research*
2023, Vol. 3, Issue 3, pp. 78-82

Inventum Biologicum

Journal homepage: www.journals.worldbiologica.com/ib

Review paper

Herbal Interventions for Urolithiasis: A Systematic Evaluation of Efficacy and Safety

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ARTICLE INFO

Article history

Received 12 August 2023
Revised 19 September 2023
Accepted 21 September 2023
Published 22 September 2023

Keywords

Urolithiasis,
Molecular mechanism,
Traditional plants,
Lead compound

ABSTRACT

Urolithiasis, the process of stone formation in the kidney, bladder, and/or urethra (urinary tract), is a condition affecting 12% of the global population, as per the World Health Organization (WHO). The prevalence is higher in males, ranging from 70-81%, compared to females, where it ranges from 47-60%, resulting in a gender ratio of 2.4:1. Traditional plants contain diverse chemical constituents that exert positive effects on lithiasis through various molecular mechanisms. Several medicinal plants, including *Moringa oleifera*, *Crataeva magna*, *Aerva javanica*, *Peperomia tetraphylla*, *Terminalia bellirica*, *Ipomoea eriocarpa*, *Punica granatum*, *Hibiscus rosasinensis*, *Costus spiralis*, and *Herniaria hirsuta*, exhibit antiurolithiatic effects. This review aims to present information and highlight current trends in research on medicinal plants with antiurolithiatic activity. The insights provided in this review may aid in the identification of lead compounds or herbal products responsible for antiurolithiatic activity.

1. Introduction

Urolithiasis is a process of forming stones in the kidney, bladder, and/or urethra (urinary tract) (Russinko et al., 2003). In urinary system, urolithiasis (Greek- ouron, “urine” and lithos, “stone”) is the condition where urinary stones are formed or located. The terms nephrolithiasis (or “renal calculus”) are stones that are present in kidney, while ureterolithiasis are stones that are in the ureter and cystolithiasis (or vesical calculi) are stones which form or have passed into the urinary bladder (Esmail Al-Snafi, 2015). Herbal interventions for urolithiasis represent a burgeoning area of interest, with researc-hers systematically evaluating their efficacy and safety. This comprehensive exploration aims to assess the effectiveness and potential risks associated with the use of herbal remedies in managing urolithiasis (Ziemba & Matlaga, 2017).

The systematic evaluation delves into various herbal interventions, scrutinizing their impact on the formation and dissolution of stones in the kidneys, bladder, and urethra. By rigorously examining the available evidence, researchers aim to discern the therapeutic benefits and safety profiles of these herbal treatments (Jayaraman & Gurusamy, 2018). Key

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DOI https://doi.org/10.5281/zenodo.7300136

considerations in this systematic evaluation include the identification of active chemical constituents within the herbs, their mechanisms of action in relation to lithiasis, and any potential adverse effects. The objective is to provide a nuanced understanding of the efficacy and safety of herbal interventions, contributing valuable insights to the field of urolithiasis management.

Through this systematic approach, the review seeks to bridge the gap in knowledge regarding herbal interventions for urolithiasis, ultimately facilitating informed decision-making in clinical practice. The synthesis of evidence surrounding efficacy and safety is crucial for healthcare professionals and researchers alike, offering a foundation for future studies and the development of evidence-based guidelines in the realm of herbal remedies for urolithiasis (Stoller, 2009).

The classification of Stones are based on their location or by their chemical composition. Calcium oxalate is the major constituent is present in urinary stones. According to survey, about 80% of kidney stones are in men when compared to women and they experience their first episode between 20-30 years of age, while for women it occurs later (Wang et al., 2017).

Over their lifetime urinary stones affect about 10% of people and prevalence increases with age, recurrence of 50% in 5-10 years and 75% within 20 years. Over the past 30 years a rapid increase have seen in women which is almost equal to that of men.

2. Pathogenesis

The volume of urine consists certain amount of calcium, phosphate, oxalate and sodium ions which is reason for formation of stones. The formation of urinary calculi is due to low urinary volume, low pH, high ion levels, and low citrate levels. The pathogenesis of stone formation includes various step physicochemical processes.

2.1 Nucleation

Nucleation of crystal occurs in unstable zone of supersaturation which is the starting stage in formation of stone due to homogeneous nucleation of a salt. Promoters induce heterogeneous nucleation leads to formation of stone and crystalluria. The reduced energy required for crystallization is provided by the promoters. Crystal components are formend due to reduced energy of solution and become part of the crystal structure. As the crystal components formed, the other crystalline particles can bind to each other and forms either an oriented or random growth pattern and then grow into a larger particle (Ratkalkar & Kleinman, 2011; Ziemba & Matlaga, 2017).

2.2 Crystal growth

In crystal growth process, the crystals can grow up by epitaxially (overgrowth of one crystalline material on to another or a substrate crystalline lattice) mediated crystal growth. Further growth of crystals is followed by monoepitaxial growth which is adsorption of the molecules or ions individually on the crystal surface from supersaturated urine leads to direct growth of one crystal on a surface of different composition or the surfaces of crystal or substrate. The growth of crystals is determined on the basis of molecular size and shape components, the physical properties, pH, and defects that may form in the crystals structure. Crystal growth is one of the major step for stone formation (Dawson & Tomson, 2012).

Aggregation After crystal growth next step is aggregation, a process in which crystal nuclei form larger particles by cohering with each other. The attractive force, result of distance in inter-particles leads to rapid aggregation. The addition of desired salts also used for growth of initial nuclei. In stone formation crystal aggregation plays a major role and is a more significant step then nucleation and growth. In aggregation, particle in solution is determined by balance of forces between aggregating effects and disaggregation effects and also a small inter particle distance that prerogative particle aggregation (Basavaraj et al., 2007).

2.3 Retention

The retention of crystal caused due to association of crystals within the epithelial cells lining. The steps in urolithiasis includes formation of crystals i.e nucleation, crystal growth followed by their retention and accumulation in the kidney. Crystal retention is one of the process for stone formation. The pathophysiology of urinary stone formation covers growth, aggregate and precipitation of crystal. The process of retention might also depend upon the composition of the renal tubular epithelial cell surface (Pareta et al., 2011).

3. Classification

3.1 Calcium stones

About 80% of urinary calculi in renal stones contain major amount of Calcium. Calcium stones are mostly found in men between the 20 and 30 years of their age. Combination of oxalate, phosphate or carbonate with calcium leads to formation of stone. Oxalate content is high in food like spinach and even found in vitamin C supplements (Alelign & Petros, 2018).

3.2 Cystine stones

Cystinuria occurs in people with high amount of cystine stones. This type of stones affects both men and women. Less than 2% of all stone types are present in cystine stone. Combination and transport of amino acid and cystine results in a genetic disorder and results in an excess of cystinuria in urinary excretions (Thomas et al., 2003).

3.3 Struvite stones

These stones are mostly found in women with urinary tract infection and increases with extent of 10– 15%. Struvite stones correlated with chronic urinary tract infection (UTI) with gram-negative, urease-positive organism that divide urea into ammonia, then the ammonia combines with magnesium and phosphate to crystalize into a calculus. Blockage of kidney, ureter or bladder occurs due to faster growth of struvite stone (Wang et al., 2017).

3.4 Uric acid stones

They are more commonly seen in women than in men. Sometimes uric acid stones occur with gout or chemotherapy. Purines with high diet containing animal protein like meat and fish, results in hyperuricosuria, low urine volume and urinary pH (pH < 5.05) exacerbates uric acid stone formation (Coe et al., 2005).

3.5 Protease-related stones

Stones of this type is usually seen in HIV positive patients due to usage of protease inhibitor indinavir sulphate drug.

3.6 Silica stones

Some silica stones are formed due to some medications like Sulfa indinavir, acetazolamide, ciprofloxacin, triamterene, ephedrine, Zonisamide, guaifenesin, laxatives (when abused), , loop diuretics, topiramate have competence to induce silica stones.

4. Sign and Symptoms

Patients with Urinary calculi report pain, infection, or hematuria. People with non-obstructing stones, small or those with staghorn calculi experience average and effortlessly controlled symptoms. Some other symptoms such as following (Aggarwal et al., 2013):

- Some symptoms like irritative voiding i.e. frequency, dysuria, suprapubic pain, urinary frequency and urgency, stranguria, bowel symptoms.
- Severe pain in lower abdomen that radiates to testicles or vulvar area, nausea with or without vomiting.
- Flank and lumbar are regions where pain radiates.
- Pain radiates anteriorly and caudally.
- Even there is pain in groin or testicle (men) or labia majora (women).
- Stones passed into bladder: Mostly asymptomatic; rarely, positional urinary retention.

Formation of Uroliths is a multifactorial process correlate with urinary tract infection, diet, decreased urinary drainage and urinary stasis, altered urinary solutes and colloids, Randall's plaque , prolonged immobilization and microliths etc.

5. Management

The treatment for stones involves reassuring care and management icludes agents such as the following (Russinko et al., 2003):

- IV hydration
- NSAIDs (eg, ketorolac, ketorolac intranasal, ibuprofen)
- Nonnarcotic analgesics (eg, acetaminophen [APAP]
- Alpha blockers (eg, tamsulosin, terazosin)
- PO/IV narcotic analgesics (eg, codeine, morphine sulfate, oxycodone/APAP, hydrocodone/APAP, dilaudid, fentanyl)
- Antiemetics (eg, metoclopramide, ondansetron)
- Antibiotics (eg, ampicillin, gentamicin, trimethoprimsulfamethoxazole, ciprofloxacin, levofloxacin, ofloxacin)

The following drug classes are used for stone prevention/chemolysis (Wang et al., 2017):

- Uricosuric agents (eg, allopurinol)
- Alkalinizing agents (eg, potassium citrate, sodium bicarbonate)

- Thiazide diuretics - help treat hypercalciuria

6. Surgical Options

Stones with size of 7 mm and larger improable to pass spontaneously that leads to serious condition which require some type of surgical procedure, such as the following (Thenmozhi et al., 2016):

- Stent placement
- Extracorporeal shockwave lithotripsy (ESWL)
- Ureteroscopy
- Percutaneous nephrostolithotomy (PCNL) or mini PNCL
- Percutaneous nephrostomy
- Open nephrostomy - largely supplanted by less-invasive techniques
- Anatrophic nephrolithotomy - for large. complex staghorn calculi that cannot be cleared by an acceptable number of PCNLs; typically done via laparoscopic or robotic approach.

As we know synthetic drugs cause various side effects, to reduce or to overcome the side effects drugs synthesized from the traditional/herbal/higher plants continue to tenant major role in modern medicine which leads to introduction of new therapeutic agents. A number of medicinal plants possessed antiurolithiatic effects these include Moringa oleifera, Crataeva magna, Aerva javanica, Peperomia tetraphylla, Terminalia bellirica, Ipomoea eriocarpa, Punica granatum, Hibiscus rosa-sinensis, Costus spiralis, Herniaria hirsute (Wang et al., 2017). This review discussed the antiurolithiatic effects of medicinal plants which has no or minimal side effects (Whelan & Schwartz, 2004).

7. Conclusion

A number of medicinal plants possessed antiurolithiatic effects. This review highlights etiology, risk factors, epidemiology, symptoms, types of kidney stones, pathogenesis, some drugs with mechanism and the antiurolithiatic effects of medicinal plants to open the door for their clinical uses as a result of effectiveness and safety.

Funding Information

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of Conflict

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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