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REVIEW OF THE PHYTOTHERAPY FOR NEPHROLITHIASIS

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Abstract

Nephrolithiasis (kidney stone) cases have a prevalence ranging from 1% to 13%. The disease not only hampers kidney function but also elevates the risk of chronic kidney diseases. The pathophysiology of nephrolithiasis is closely linked to elevated concentrations of calcium, oxalate, and/or uric acid in the urine. Pharmacotherapy to manage nephrolithiasis includes thiazide diuretics, allopurinol, citrate supplements, and alpha-blockers that have been prescribed to relieve symptoms. In addition, there is growing interest in exploring the potential of phytotherapy. This review aims to identify suitable phytotherapy approaches by examining relevant articles on nephrolithiasis. The research methodology involved searching PubMed articles using the keywords of ((("Plant Extracts") AND ("Nephrolithiasis")) OR ("Ureterolithiasis"). The articles obtained from the initial search were n =123. 2 authors screened articles for their eligibility. The inclusion criteria were limited to articles written in English, topics related to nephrolithiasis and not other kidney diseases, the botanical names of the plants and the method of extraction are clearly described, complete studies with clear descriptions regarding the methods and results, not synthetic drugs, and not involving medical instruments or laser to remove the stones. Articles included in the review were n = 17. Water and hydro-alcohol were the solvents used to extract the plants. Twenty-two plants have confirmed their anti-nephrolithiasis activity, and nine articles described the assay by *in vivo* study, two by *in vitro* study, three by both *in vitro* and *in vivo* study, and only one article mentioned a study in humans by a randomized-control trial on a mixture of herbs. It is concluded that *Rhizoma alismatis, Poria cocos, Polyporus umbellatus, Atractylodis macrocephalae*, and *Cinnamomi Cassiae* prepared as a mixture in the Wu-Ling-San formula have a potential therapeutic effect on nephrolithiasis, as this formula has been studied in humans.

Keywords: nephrolithiasis, phytotherapy, plants

Introduction

Nephrolithiasis, a widespread disease in both developed and developing countries, has a prevalence ranging from 1% to 13% and is known as the peril for other disorders, e.g., diabetes mellitus, cardiovascular disease, and chronic kidney disease.[1-3] In Asia, nephrolithiasis is 5–19.1%. It was described that malnutrition and water deprivation contribute to increasing incidence in developing countries. In contrast, increased salt and protein intake is the main cause of nephrolithiasis in developed countries.[3] The increasing prevalence of this condition poses a significant threat to public health and the well-being of affected individuals. Metabolic dysfunction and dietary habits are the main factors contributing to this rise. The formation of kidney stones not only hampers kidney function but also elevates the risk of chronic kidney diseases (CKDs). These stones are predominantly found in men and typically lead to acute complications, including flank and abdominal pain, hematuria (blood in urine), and urinary infections.[2] Another symptom, such as intermittent renal colic, which can lead to chronic kidney disease and loss of kidney function, was also reported. In addition to inducing pain and high medical costs, nephrolithiasis also causes serious complications, such as depression.[4,5] The impact of pain on quality of life (QoL) was highest in patients with frequent stone episodes. Therefore, nephrolithiasis is considered to truncate the quality of life.[4]

Calcium is the most common type of stone found in about 80% of cases of nephrolithiasis, constituted principally in the form of calcium oxalate or calcium phosphate. The other types are uric acid, struvite (magnesium ammonium phosphate), and cystine stones.[6] The formation of kidney stones is believed to be influenced by a combination of genetic and environmental elements, such as inadequate hydration due to limited fluid consumption, as well as a high intake of dairy protein and salts,[3,8] which are also believed to be the risk factors for cardiovascular disease (CVD) and diabetes mellitus (DM).

Advances in the clinical management of kidney stones have led to the development of extracorporeal shock wave lithotripsy, which is currently the main approach in treating nephrolithiasis. This procedure utilizes shockwaves to degrade the calcium stones and thus can be excreted through the urinary tract. However, lithotripsy is an expensive procedure and is often followed by a high recurrence rate of kidney stones. Therefore, a preventive approach is needed to reduce the formation of kidney stones.[5]

The identification of the stone influences effective nephrolithiasis prevention. Preventive strategies that include modification in meals (dairy meat restriction) and/or pharmacotherapy (e.g., hydrochlorothiazide at 25–50 mg/day in adults and 0.5–1 mg/kg/day in pediatrics) may be required. In addition, regardless of underlying etiology, increasing water intake to maintain an optimum urine output and a low salt diet should be implemented as a daily practice.[6.7] Over the past twenty years, Significant advancements have been achieved in surgical procedures for extracting kidney stones. However, it is common for patients to encounter a relapse of the condition following the surgery.[5,6] Additionally, numerous epidemiological studies have established a connection between kidney stone occurrence and increased susceptibility to cardiovascular disorders, such as coronary heart disease and stroke. Consequently, it is imperative to conduct a thorough exploration to comprehend the underlying mechanisms of nephrolithiasis or kidney stones and to develop effective strategies for prevention and treatment.

Despite the pharmacotherapy to manage nephrolithiasis, there is growing interest in exploring the potential of phytotherapy. There are very few review articles on herbal medicines in managing nephrolithiasis. Only two reviews describe it; thus, we believe our review will give readers more insight into identifying suitable phytotherapy approaches for nephrolithiasis.

Methods

Articles used in this study were accessed via a single database, PubMed database (*https://pubmed.ncbi.nlm.nih.gov/*), filtered to 10 years of publication date, and free full-

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texts. The search was conducted from May 2023 to June 2023 using the Boolean operators "AND" and "OR": ((Plant Extract) AND (Nephrolithiasis) OR (Ureterolithiasis)). The articles obtained from the initial search were 123 studies. 2 authors screened articles for their eligibility. The inclusion criteria were limited to articles written in English, topics related to nephrolithiasis and not to other kidney diseases, the botanical names of the plants and the method of extraction are clearly described, complete studies with clear descriptions regarding the methods and results, not synthetic drugs, and not involving medical instruments or laser to remove the stones. Articles included in the review were n = 17. The flowchart of the article search is summarized in Figure 1.

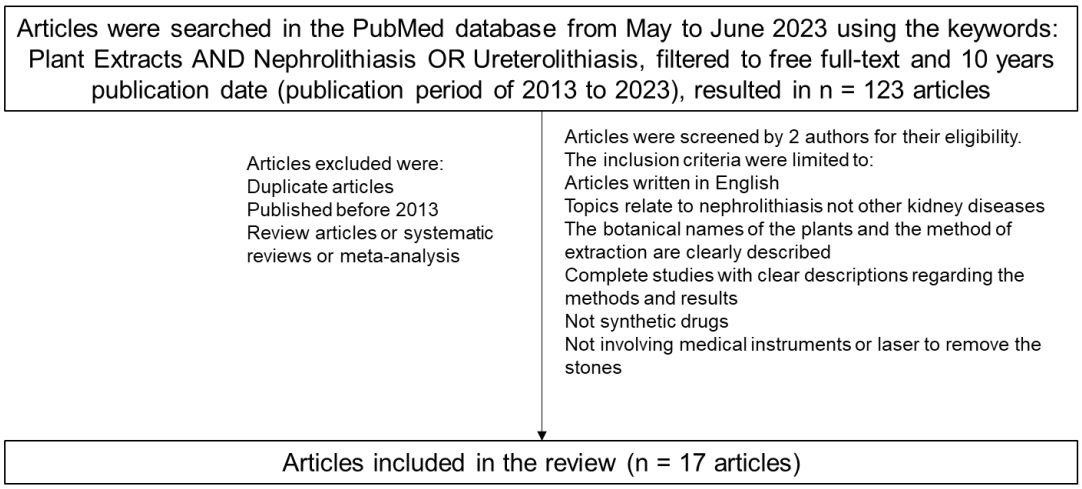

Figure 1. The flowchart of the article search

Results

Phytotherapy of Nephrolithiasis

Phytotherapy for nephrolithiasis serves to minimize the side effects given by drugs or after surgery to prevent recurrence or worsen the condition of the kidneys. However, our literature study on phytotherapy for nephrolithiasis found that it was mostly carried out by *in vitro* and *in vivo* studies, and only one article describes a study in humans in the publication period of 2013 to 2023. There were 11 articles elaborating on the effects of fruit extracts on managing nephrolithiasis, but these articles were published from 1993 to 2008 and thus cannot be included in this review.[8-18] The summary of plants used to manage nephrolithiasis by *in vitro*, *in vivo*, and human study is tabulated in Table 1.

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Table 1. Plants Used to Manage Nephrolithiasis By *In Vitro*, *In Vivo*, and Human Study

Reference	Name of Plant	Part of Plant	Solvent Used for Extraction	Dose or Concentration	Type of Study	Result	Side Effects
19	*Apium graveolens* L.	Herbs	Hydro-alcohol	600 mg/kg BW	*In vivo*	*A. graveolens* extract showed stronger anti-nephrolithiasis activity than apigenin.	No side effects
20	*Polygonum aviculare* L.	Leaf	Water	100 and 400 mg/kg BW	*In vivo*	Saponins and flavonoids in the extract revealed antioxidant, antibacterial, and diuretic effects.	No side effects
21	*Garcinia cambogia*	In the form of a commercial extract	Not described	1500 mg	*In vivo*	The extract efficiently removes calcium oxalate stones	Not described
22	*Eryngium campestre*	Aerial part	Water	100, 200, and 400 mg/kg	*In vivo*	*E. campestre* decreased crystal deposition in the kidney of the hyperoxaluric rat.	Not described

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Table 1. (Extension)

Reference	Name of Plant	Part of Plant	Solvent Used for Extraction	Dose or Concentration	Type of Study	Result	Side Effects
23	*Taraxacum officinale*	Dried aerial part	Water	Extract (4 and 8 mg/mL), and potassium citrate (150, 200, and 350 mg/mL)	*In vitro*	*T. officinale* extract showed strong anti-nephrolithiasis activity comparable to that of potassium citrate.	No side effects
24	*Urtica dioica* and *Tribulus terrestris*	Powder	Hydro-alcohol	*Urtica dioica* at dose 1400 g/kg BW *Tribulus terrestris* at dose 200 mg/kg BW	*In vivo*	The extracts reduced the level of urinary oxalate.	No side effects
25	*Tribulus terrestris*	Dried and matured fruits	Water	The maximum dose of 750 mg/kg BW	*In vivo*	The extract revealed potential prophylactic and curative abilities against experimentally induced nephrolithiasis	No side effects

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Table 1. (Extension)

Reference	Name of Plant	Part of Plant	Solvent Used for Extraction	Dose or Concentration	Type of Study	Result	Side Effects
[26]	*Paeoniae alba*	Roots	Water	220 mg/kg BW for *in vitro* 660 mg/kg BW for *in vivo*	*In vitro* and *in vivo*	The extract prevented kidney stone formation.	No side effects
[27]	*Ceterach officinarum*	Dried leaves and aerial parts	Water	Not described	*In vitro*	The extract showed high antioxidant power and is a potent inhibitor of calcium oxalate aggregation.	Promotes the formation of calcium oxalate dihydrate
[28]	*Musa paradisiaca*	Pseudostem	Hydro-alcohol	250 mg/kg BW	*In vivo*	The extract reduced oxalate concentration in urine crystal deposition	No side effects
[29]	*Bergenia ligulata*	Dried and powdered rhizome	Water and dichloromethane	185 mg/kg BW of water extract 7 mg/kg BW of dichloromethane fraction	*In vitro* and *ex vivo*	The extracts showed curative properties against urolithiasis.	No side effects

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Table 1. (Extension)

Reference	Name of Plant	Part of Plant	Solvent Used for Extraction	Dose or Concentration	Type of Study	Result	Side Effects
30	*Desmodium styracifolium*, *Plantago asiatica, Pyrrosia calvata*, and *Zea mays*	Herbs with a fine powder formula	Hydro-alcohol	1.35 g/kg BW and 2.7 g/kg BW	*In vivo*	The extract increased the levels of E-cadherin and CK18 and decreased vimentin levels in varying degrees. It also reduced the expression of CaOx-induced fibrosis marker collagen II.	No side effects
31	*Vitis vinifera*	Red grape seeds and white grape seeds (polyphenol)	Water	200 mg/L	*In vivo*	The extract prevented COM papillary calculi by avoiding papillary tissue injury caused by cytotoxic substances with an oxidative capacity.	No side effects

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Table 1. (Extension)

Reference	Name of Plant	Part of Plant	Solvent Used for Extraction	Dose or Concentration	Type of Study	Result	Side Effects
32	*Cissus gongylodes*	Leaf	Water	150 mg/mL	*In vivo*	The extract inhibited the main inflammatory pathways and dissolved the most prevalent types of crystals in urolithiasis.	No side effects
33	*Angelica sinensis*	The dry roots (polysaccharide)	Water	80 and 320 mg/kg/day	*In vitro* and *in vivo*	The extract inhibited calcium oxalate crystallization *in vitro* and possessed anti-urolithiasis effects *in vivo.*	No side effects
34	*Launaea procumbens*	Dried leaves	Hydro-alcohol	150 and 300 mg/kg BW	*In vivo*	The extract is effective against urolithiasis.	No side effects

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Table 1. (Extension)

Reference	Name of Plant	Part of Plant	Solvent Used for Extraction	Dose or Concentration	Type of Study	Result	Side Effects
35	*Rhizoma alismatis*, *Poria cocos*, *Polyporus umbellatus*, *Atractylodis m*acrocephalae, and *Cinnamomi cassiae*	Herbs with a fine powder formula (Wulingsan)	Water		Study in human (Randomized Clinical Trial)	The herbal mixture revealed better effects than loop diuretics.	Increased urine volume

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Discussions

Pathophysiology of Nephrolithiasis

The composition of urine can be used to predict the composition of kidney stones. Kidney stones can form when the urine contains higher calcium, oxalate, and/or uric acid concentrations. If there is an excess of calcium, it can lead to calcium stones; if there is an excess of uric acid, it can result in uric acid stones; and if there is an excess of oxalate, it can lead to oxalate stones. Among all types of kidney stones, calcium oxalate accounts for 74% of cases, calcium phosphate for 20%, and uric acid for 4%. The remaining stones are cystine and magnesium ammonium phosphate (struvite) stones. Generally, smaller kidney stones can pass through the urinary tract without intervention. However, as the size of the stones reaches 7 mm or larger, they often require medical intervention for removal. Kidney stones that are 5 mm or smaller usually pass naturally, but due to variations in individuals' anatomy, some patients may struggle to pass even small stones.[36]

Pharmacotherapy of Nephrolithiasis

Thiazide diuretics are medications that can lower calcium concentration in the urine by inhibiting calcium reabsorption in the renal tubules. This is particularly beneficial for individuals with hypercalciuria, a condition characterized by high calcium levels in the urine. By reducing calcium concentration, the risk of forming calcium stones can be diminished. Thiazide diuretics increase sodium reabsorption in the renal tubules, leading to higher levels of sodium in the urine and a decrease in the concentration of oxalate. Oxalate is a key component in the formation of oxalate stones. Thus, reducing its concentration may help prevent their development. Additionally, thiazides exhibit their diuretic action by inhibiting the Na^+/Cl^- cotransporter in the distal convoluted tubule of the kidney. When this channel is blocked, reduced levels of Na^+ move the luminal membrane, thus lessening the work of the Na^+/K^+ pump and reducing the flow of Na^+ and H_2O to the interstitium. The reduction in urine volume leads to an increase in stone formation since higher volumes of urine help dissolve stone-forming substances like calcium and oxalate more effectively. Examples of thiazide diuretic medications include hydrochlorothiazide (HCTZ), chlorthalidone, and indapamide.[37,38]

Allopurinol works by inhibiting xanthine oxidase, which reduces the production of uric acid in the body. By lowering the concentration of uric acid, allopurinol can help prevent the formation of new uric acid stones or the growth of existing ones. This reduces the risk of developing urate stones and can decrease pre-existing stones' size. Nephrolithiasis associated with hyperuricosuria can cause kidney damage and long-term complications. Allopurinol helps protect the kidneys from further harm by controlling uric acid levels.[39]

Citrate supplements, such as potassium citrate or sodium citrate, are used as part of the treatment for nephrolithiasis. Their primary purpose is to decrease the concentration of urinary oxalate, which helps prevent the formation of oxalate stones and reduces the risk of nephrolithiasis. Additionally, citrate supplements can increase urine pH, which inhibits the formation of uric acid stones.[38,39]

Alpha-blockers are a class of medications used to treat nephrolithiasis to manage symptoms and facilitate the passage of stones through the urinary tract. These drugs work by blocking the action of the hormone noradrenaline on the alpha-adrenergic receptors in the urinary tract muscles. By doing so, they induce relaxation in the muscles of the urinary tract, including the muscles in the ureters, which are the tubes connecting the kidneys to the bladder. This relaxation helps widen the urinary tract, making it easier for stones to pass through. Alpha-blockers can also alleviate pain and muscle spasms caused by the movement of stones through the urinary tract. By reducing muscle spasms, these

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medications relieve the painful symptoms associated with nephrolithiasis. Examples of commonly used drugs in the treatment of nephrolithiasis are tamsulosin and alfuzosin.[38]

Phytotherapy for Nephrolithiasis in Animals

Nineteen plants, namely *Atractylodis macrocephalae, Angelica sinensis, Apium graveolens* L., *Bergenia ligulata, Ceterach officinarum, Cinnamomi cassia, Cissus gongylodes, Desmodium styracifolium, Eryngium campestre, Garcinia cambogia, Launaea procumbens, Musa paradisiaca, Paeoniae alba, Plantago asiatica, Polygonum aviculare L., Polyporus umbellatus, Poria cocos, Pyrrosia calvata, Rhizoma alismatis, Taraxacum officinale, Tribulus terrestris, Urtica dioica, Vitis vinifera,* and *Zea mays,* were reported for their anti-nephrolithiasis activity (Table 1). No side effects were reported, revealing the safety of these plants in animal models.

Phytotherapy for Nephrolithiasis in Humans

Only one article reported a randomized clinical trial of phytotherapy using the Wulingsan formula (contains *Rhizoma alismatis*, *Poria cocos*, *Polyporus umbellatus*, *Atractylodis m*acrocephalae, and *Cinnamomi* cassiae) for nephrolithiasis. In this prospective, randomized, and placebo-controlled clinical trial, all participants (n = 39) with recurrent calcium oxalate nephrolithiasis were asked to consume sufficient water to urinate a minimum of 2 L per day during the study period. A 24-hour urine collection was conducted to establish the baseline levels of multiple urinary parameters before the Wulingsan intervention.[35] Managing nephrolithiasis with Wulingsan was first recorded in a book during the Ming Dynasty.[40] Moreover, an *in vivo* study in rats reported that Wulingsan could suppress the development of kidney hydroxylapatite calcinosis in rats fed a high phosphorus diet.[41]

Wulingsan was reported to possess better effects than loop diuretics because this herbal mixture therapy could elevate urine volume without causing electrolyte imbalance.[35] Loop diuretics work by competing with Cl^- to bind to the Na-K-2Cl (NKCC2) cotransporter at the apical membrane of the ascending loop of Henle and inhibiting the cotransporter, which prevents the reabsorption of Na+ and Cl^-, thus decreasing tonicity in the interstitium, and increasing free water excretion.[42]

Conclusion

Nephrolithiasis is commonly treated with thiazide diuretics, citrate supplements, alpha-blockers, and allopurinol. Nineteen plants were studied *in vitro* and *in vivo* and had been confirmed for their anti-nephrolithiasis activity. The limitation of this review is that there are no side effects resulting from *in vivo* or *in vitro* studies. Only one article describes a randomized clinical trial study of the Wulingsan formula (contains *Rhizoma alismatis*, *Poria cocos*, *Polyporus umbellatus*, *Atractylodis m*acrocephalae, and *Cinnamomi* cassiae) in humans within the publication period of 2013 to 2023. Thus, it has been selected as the best phytotherapy. This formula was reported as better than loop diuretics or thiazide diuretics. However, the administration of this Chinese herbal formula should be monitored because it increases urine volume, and the effects of long-term use have not been studied. This review unveils the challenge of exploring phytotherapy for nephrolithiasis in humans.

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