

Effectiveness of Herbal Medicine in Renal Lithiasis: A Review

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ABSTRACT

The renal lithiasis is a frequent disease that affect between 4-15% of worldwide population with a high percentage of recurrences. The composition of the stone is variated, but, more than 80% of uroliths are of calcium oxalate. The mechanisms involved in the formation of calcific stones are not fully understood and the available treatment not permit the prevention and destruction of the stones at same time. For these reasons, many studies have been focused to understand the mechanism involved in the renal lithiasis and in the development the new drugs for the treatment and prevention of this pathology and its recurrences. In this paper, it is shown a review about formation of calcific stones, their treatment and the effectiveness of the herbal medicine as alternative treatment. Also, a list of antilithiatic remedies of cuban herbal medicine is showed.

Keywords: Renal lithiasis; pharmacology; therapeutic; herbal medicine (Siriraj Med J 2020; 72: 188-194)

INTRODUCTION

Renal lithiasis can be defined as the deposition of stones in urinary tract due to an alteration of the normal crystallization conditions of urine.¹ It is explained through of the loss of the equilibrium between promoters and inhibitors of the crystallization,² urine composition and renal morphoanatomy.³

Currently, it is the third most frequent urological disease after urinary tract infections and prostate problems.⁴ It has a prevalence that ranges between 4-15% of the world population⁵ and a high recurrence rate, that is, the probability of repeating a renal lithiasis episode is 40% after 5 years of the first calculi and 60% after 10 years.⁶ It is a health problem with greater incidence in people between 30-60 years of age and more common in men than in women.⁷

The difference in prevalence between countries is associated with the combination of genetic and environmental factors, including dietary habits, climatic conditions and socio-economic status.⁴ For example, several studies show that the incidence is higher in populations of warm countries compared to populations in cold countries. It has also been found that high consumption of salt, animal protein, calcium, fatty acids and sugar are risk factors for the development of kidney stones.^{4,7} Finally, renal lithiasis has been associated with a family history of kidney stones and with some diseases such as diabetes, hypertension, hyperthyroidism, obesity, metabolic syndromes, gout and urinary tract infections.^{4,8}

The stones may be composed of calcium phosphate, uric acid, struvite, cystine and oxalate calcium. The oxalate stone are the most frequent, being present in

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more than 80% of the uroliths.⁸ For this reason, this study will focus on oxalate stones.

The mechanisms involved in the formation of calcific stones are not fully understood.⁵ It is generally agreed that urinary lithiasis is a multifaceted biological process that involves physicochemical changes and supersaturation of urine⁹ leading to crystal nucleation, aggregation and growth of insoluble particles.¹⁰

For the treatment of renal stones minimally invasive surgery is used, it's effectiveness to broke the calculi but it has not reduced recurrence rates.^{7,10} On the other hand, many drugs have been used, such as, thiazide diuretics, potassium citrate, non-steroidal anti-inflammatory drugs (NSAIDs); but they're only used for prevent or treat the symptoms.^{7,8,10}

For these reasons, many studies have been focused to understand the mechanism involved in the renal lithiasis and in the development the new drugs for the treatment and prevention of this pathology and its recurrences. Herein, in this paper, it is shown a review about formation of calcific stones, their treatment and the pharmacological models to study of the antilithiatic activity in oxalate stone.

Formation of renal stones

The mechanisms involved in the formation of calcific stones are not fully understood.⁵ Renal stone formation is a biological process that involves physicochemical changes and supersaturation of urine.⁹ It is explained through of the loss of the equilibrium between promoters and inhibitors of the crystallization,² urine composition and renal morphoanatomy.³

Recently, the promoters and inhibitors of the urine has been referred as modulators, which can be small molecules or low-molecular weight that modify supersaturation of the urine by serving as chelators of calcium and oxalate by forming soluble complex. The formation of this complex depends on numerous physicochemical factors such as the concentration of individual (competing) chemical species, the relative magnitude of the formation constants of the complexes themselves, the pH and ionic strength of the urine in which the process occurs.¹¹ As a result of supersaturation, solutes precipitate in urine leads to nucleation and then crystal concretions are formed.⁹

The first step in the formation of kidney stone begins by the formation of nucleus (termed as nidus), normally of apatite (calcium phosphate) due to that the heterogeneous nucleation is easier than homogeneous nucleation in physiological conditions of the urine.¹² It is the transformation from a liquid to a solid phase in a supersaturated solution.¹³ A widely held theory is that

of Randall's plaques, which proposes that subepithelial interstitial calcium-based deposits act as nuclei for stone formation. These plaques originate adjacent to the thin limbs of loops of Henle as spherical particles, which could be related to the high local ion concentrations at this site, and can extended to the interstitium.¹⁴⁻¹⁶ Recent studies have investigated the role of oxalate-degrading bacteria. These form apatite structures that serve as a crystallization center for the formation of stones and could be a pharmacological target to avoid the nucleation process. Also, existing epithelial cells, urinary casts, RBCs, and other crystals in urine too can act as nucleating centers in the process of nuclei formation termed as heterogeneous nucleation.⁹

The growth process is very important due to the small stones are expelled by urine, but the big stones require medical treatment. Its mechanism is simple because only requires the addition of new particles of the urine.¹² This process can be favored by the retention of microcrystals in the urothelium and controlled by the lithogenesis inhibitors.^{3,17} Recent studies have demonstrated that oxalate produce damage to renal cell by the generation of reactive oxygen species¹⁸; which increase the surface expression of phosphatidylserine, sialic acid, hyaluronan, osteopontin, or the glycoprotein receptor CD44, resulting in more crystal adhesion and formation of the nidus for the formation of stone.⁵ On the other hand, the presence of renal cavities with low urodynamic efficacy retain urine by long periods of time in the upper urinary tract, which favors the formation of stone.¹⁹ Finally, there are substances in the urine act as inhibitors of lithogenesis through of the inhibition in the crystal surface; also, there substances have complexing properties with some ions involved in the precipitation process decreasing its concentration.¹² Several inhibitors have been found in the urine as citrate, phytate, magnesium and pyrophosphate ions³ and other molecules as uropontin, osteopontin, bikunin, and Tamm-Horsfall protein¹⁵; but citrate, magnesium and phytate have been the most studied.¹⁹⁻²⁰

Treatment of renal stones

The treatment of the calculi will depend of their size and site, and of any symptoms and signs, particularly of obstruction. When the stones are less than 10 mm can be expelled with pharmacologic treatment, but, when the calculi are higher than 10 mm or can't be expelled with pharmacologic treatment, it is necessary to use of minimally invasive surgery,^{8,14} such as extracorporeal shockwave lithotripsy (ESWL), percutaneous nephrolithotomy (PCNL), or ureteroscopy (URS), which has revolutionized acute and complex stone management.⁵ The problem

is that these techniques don't prevent the likelihood of new stone formation because often result in incomplete stone clearance.^{5,10,18} Then, to reduce the rate of stone recurrence is necessary the intervention in the form of lifestyle advice and some forms of medical therapy.⁵ For example, the increase of liquid, potassium, magnesium, calcium, vegetable and fruit intake and the decrease of sodium, animal protein and fat consumption has been associated with reduction of renal stone.^{1,7,14,21,22} On the other hand, many drugs have been used to prevent the recidives, for example, thiazide diuretic, potassium citrate, allopurinol, NSAIDs, calcium antagonist, pyridoxine, alfa-blockers.^{8,14,21,22} However, the scientific evidence about the efficacy of the pharmacologic therapy is less convincing.^{10,17,23} All these facts indicate the need for new therapeutic approaches for the treatment of renal stones,¹⁸ therefore, new alternatives are being tested using herbal medicine or phytotherapy.¹⁷

Traditional medicine in renal lithiasis: a therapeutic solution?

The use of medicinal plants dates from the beginnings of humanity, when people had no other effective therapeutic resources to treat their diseases. This knowledge was transmitted through legends, pictographs and various monographs until our days.²⁴ The oldest written evidence of medicinal plants' usage for preparation of drugs has been found on a Sumerian clay slab from Nagpur, approximately 5000 years old. Other ancient references were showed

in «The Chinese book on roots and grasses» written by Emperor Shen Nung around 2500 BC, «The Indian holy books Vedas» and «The Ebers Papyrus», written about 1550 BC.²⁵

According to data from the World Health Organization (WHO), 80% of the world's population uses plants as a remedy to cure their diseases.²⁶ On the other hand, it is known that around 20% -30% of the medicines available in the market are derived from natural products.²⁷

Recently the use and commercialization of medicinal herbs has increased in developed and developing countries, linking several multinational companies, which have obtained benefits of up to \$ 7.00 billion in Europe, \$ 3.2 billion in the United States and \$ 2.3 billion in Asia (Table 1). The reasons for this increase are due to the preference of consumers for natural therapies; concern regarding undesirable side effects of modern medicines and the belief that herbal drugs are free from side effects, since millions of people all over the world have been using herbal medicines for thousands of years; great interest in alternative medicines; preference of populations for preventive medicine due to increasing population age; the belief that herbal medicines might be of effective benefit in the treatment of certain diseases where conventional therapies and medicines have proven to be inadequate; tendency towards self-medication; improvement in quality, proof of efficacy and safety of herbal medicines and high cost of synthetic medicines.²⁸

TABLE 1. Richness obtained from sales of herbal medicines in some countries in the year 1996.

Country	Incomes (USD)
Germany	\$3.5 billion
United States of America	\$3.2 billion
Japan	\$2.1 billion
France	\$1.8 billion
Italy	\$700.0 million
United Kingdom	\$400.0 million
Spain	\$300.0 million
Netherlands	\$100.0 million

The best acceptance of the population of herbal medicine, the wide traditional knowledge about medicinal plants, the few scientific studies that support the therapeutic properties of these and the interest of the pharmaceutical industry in the development of phytopharmaceuticals constitute opportunities in the research of herbal medicines as therapeutic alternatives for several diseases, especially in those in which conventional medicine has not been very effective. On the other hand, herbal medicines usually contain a range of pharmacologically active compounds. This could be an advantageous characteristic for the therapeutic application of herbal medicine, since sometimes beneficial synergisms are established in the treatment of some diseases, being able to be more effective than synthetic drugs.

As mentioned earlier, several researchers have focused their attention on herbal medicine for the treatment of renal lithiasis because, currently, this pathology is treated by minimal access surgery and pharmacological therapy is less convincing.

The traditional knowledge about medicinal plants is the first clinical evidence on efficacy of herbal medicine, however, scientific studies are necessary to corroborate the ethnobotanical information.²⁸ Recently, a list of antilithiatic plants used by population of different countries of the world was published, where already 500 species belonging to 106 families were identified. The families more representative in this study were Asteraceae (87), Fabaceae (71), Lamiaceae (58), Rubiaceae (17), Solanaceae (12), Phyllanthaceae (9), Zingiberaceae (9), Rutaceae (9), Polygonaceae (8) and Urticaceae (8).²⁹⁻³¹ Other reported families were Rosaceae (41), Poaceae (24), Malvaceae (23), Brassicaceae (20) and Boraginaceae (13).³²⁻³³ The wide traditional knowledge of antilithiatic plants favors the researches of herbal medicine in this pathology because it increases the chances of finding an effective therapeutic treatment.

Cuban herbal medicine and renal lithiasis

In Cuba, the first evidence about the use of medicinal plants was found in the primitive community, where “el behíque” was the second most important person into the community. Among its functions was the treatment of patients through remedies made with medicinal plants.³⁴ On the other hand, in the wars of independence (XIX century), “los mambises” found in the Cuban flora a solution to the cure of their wounds and diseases. For example, José Martí mentioned in his Campaign Diary the benefits of “hijereta”, “cilantro” honey and other remedies used in camps.³⁵ In 1945, the Cuban

scientist Juan Tomás Roig published his book «Plantas Medicinales y Aromáticas de Cuba» where he described more than five thousand medicinal species used by the Cuban population.³⁶ Recently, the Ministry of Public Health of Cuba created the National Program of Natural and Traditional Medicine and elaborated the National Therapeutic Guide of Phytodrugs and beer-derived products for its application in health institutions.

The great variety of medicinal plants in the Cuban flora, together with the widely ethnobotanical knowledge increases the opportunities for the search of new therapies in the treatment of various diseases, of which, the renal affections have been one of the most treated in the ethnobotany. However, the phytotherapeutic potential of the island is still virgin. For example, in ethnobotanical studies made in Cuba, one hundred seventy-nine species have been used in the renal system, of which only 9% have been evaluated pharmacologically.³⁷⁻³⁹ Table 2 shows a compilation of some plants used for the treatment of kidney stones according to ethnobotanical studies carried out in different areas of the country.

Bashir and Gilani (2009) demonstrated the antilithiatic activity of the methanol 30% extract from *Bergenias ligulata* using *in vitro* and *in vivo* studies. The extract showed capacity to evade the crystallization trough *in vitro* calcium oxalate crystallization test. Also, the capacity to decrease the renal damage produced by oxalate crystals through generation of Reactive Oxygen Species (ROS) was corroborated by DPPH assays. The diuretic activity and antilithiatic activity of the extract was demonstrated in Wistar rats.⁴⁴ After that, the authors evaluate the antilithiatic activity of Berberine, an alkaloid described for this plant, and they obtain similar results to the methanol 30% extract.¹⁰ A similar study was done in *Selaginella lepidophylla*, but, in this case the antilithiatic activity was related with the presence of polyphenols and flavonoids in the plant.¹⁷ The antilithiatic effect of other medicinal plants used by population, such as, *Costus spiralis*, *Phyllanthus niruri*, *Origanum vulgare*, *Hibiscus sabdariffa*, *Zea mays*^{10,45}, *Berberis trifoliata*⁴⁶, *Punica granatum*²³ and *Terminalia arjuna*⁵ has been demonstrated with promissory results. Generally, this effect has been attributed to polyphenols⁴⁷ and flavonoids.⁴⁸

The ethnobotanical use and the scientific evidence about the mechanism of action and related chemical compound with antilithiatic activity is a proof of the effectiveness of the medicinal plant in the treatment of this pathology, however, the controlled clinical trials are required. Then, future studies should be leaded in this way.

TABLE 2. Herbal medicine used by Cuban population to treat the lithiasis renal.

Plant	Family	Commun name	Part(s)	Preparation	Ref.
<i>Blechnum pyramidatum</i>	<i>Acanthaceae</i>	Mazorquilla	Aerial	Decoction	[39]
<i>Caesalpinia bahamensis</i>	<i>Caesalpinaceae</i>	Brasilete	Stem	Decoction	[40]
<i>Chiococca alba</i>	<i>Rubiaceae</i>	Bejuco verraco	Root	Decoction	[41]
<i>Cymbopogon citratus</i>	<i>Poaceae</i>	Caña de limón	Stem	Decoction	[40]
<i>Cyperus rotundus</i>	<i>Cyperaceae</i>	Caramamá	Root	Decoction	[41]
<i>Erythroxylum havanense</i>	<i>Erythroxylaceae</i>	Jibá	Root	Decoction	[41]
<i>Guazuma ulmifolia</i>	<i>Sterculiaceae</i>	Guásima	Bark	Decoction	[41]
<i>Heliotropium angiospermum</i>	<i>Boraginaceae</i>	Alacrancillo	Leaves	Infusion	[40]
<i>Lepidium virginicum</i>	<i>Brassicaceae</i>	Matuerzo	Leaves	Decoction	[42]
<i>Lonchocarpus pentaphyllus</i>	<i>Fabaceae</i>	Guamá amarillo	Stem, Root	Decoction	[39]
<i>Momordica charantia</i>	<i>Cucurbitaceae</i>	Cundeamor	Leaves	Infusion	[40]
<i>Peperomia pellucida</i>	<i>Piperaceae</i>	Corazón de Hombre	Aerial	Decoction	[41]
<i>Polypodium polipodioides</i>	<i>Polypodiaceae</i>	Doradilla	Leaves	Decoction	[39]
<i>Rystonea regia</i>	<i>Arecaceae</i>	Palma real	Root	Decoction	[40]
<i>Salpianthus purpurascens</i>	<i>Bignoniaceae</i>	Nitro	Aerial	Decoction	[40]
<i>Trichilia glabra</i>	<i>Meliaceae</i>	Siguaraya	Leaves	Infusion	[40]
<i>Urera baccifera</i>	<i>Urticaceae</i>	Chichicate	Root	Decoction	[40]
<i>Xanthium strumarium</i>	<i>Asteraceae</i>	Guizaso de caballo	Root	Decoction	[40]
<i>Xiphidium coeruleum</i>	<i>Haemodoraceae</i>	Cola de paloma	Leaves	Infusion	[43]
<i>Zea mays</i>	<i>Poaceae</i>	Maíz	Hair	Infusion	[40]

DISCUSSION

Renal lithiasis is an important global renal problem due to its high incidence and the lack of effective pharmacological treatments. Until now, the minimally invasive surgery is the only option to destroy the renal calculi. Then, the search for new therapeutic alternatives continues being a topic of interest in the scientific community, where medicinal plants have gained an important place on research in this field. Despite the widespread use of plants in traditional medicine, their therapeutic application is limited due to the lack of scientific studies that support their therapeutic properties, especially clinical studies.²⁸ However, a study

done by Newman & Cragg, (2016) shows that 50% of the drugs approved in the period 1981 to 2014 originated in natural products.⁴⁹ This evidence shows that plants are an effective resource for the treatment of diseases, however, studies that support their use in therapeutics are required, which is one of the weaknesses in the clinical application of herbal medicine. On the other hand, several *in vitro*, *in vivo* and clinical studies have been developed in plants traditionally used for the treatment of renal lithiasis with promising results, however, the phytochemical studies of the plants have been insufficient. As a consequence, the validity of the studies is limited because without

phytochemical characterization, quality control is difficult and reproducibility of results questionable. The available information shows that some possible mechanisms of action of plant extracts include an increased excretion of urinary citrate, decreased excretion of urinary calcium and oxalate, ability to inhibit the crystallization process of oxalate calcium or could be attributable to diuretic, antioxidant or antibacterial effects.⁵⁰

Summarizing, the best acceptance of natural products in the world population, the interest of the pharmaceutical industry in the development of these, the traditional knowledge of a great variety of plants for the treatment of lithiasis and the promising results of the scientific studies carried out are elements that support the theory that plants could be an effective therapeutic resource for the treatment of renal lithiasis, however, still requires phytochemical and biological studies that reinforce this theory.

CONCLUSION

The higher incidence and prevalence of renal lithiasis and the lack of an effective pharmacological therapy for its treatment are focused of attention for several researchers in the development of new drugs, being the natural products a potential source of bioactive molecules for this pathology.

Conflict of Interest: The authors declare not conflict of interests.

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