

## MEDICAL MANAGMENT OF UROLITHIASIS, WHAT OPORTUNITY FOR PHYTOTHERAPY?

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### 1. ABSTRACT

Urolithiasis is the formation of stones in the urinary tract, causing pain and bleeding, and may lead to secondary infection. It is the third most common affliction of the urinary tract. Of many types of stones that are formed, the most common are calcium oxalate. The formation of such concretion encompasses several physico-chemical events beginning with crystal nucleation, growth, aggregation, and ending by retention within urinary tract. The mechanisms governing the induction of all these processes remain speculative. One of the important phenomena that characterizes urolithiasis is its high recurrence. Thus, a protective system is required including extracorporeal shock wave lithotripsy and medicament treatment. Unfortunately, these means remain costly and in most cases are invasive and with side effects. Therefore, it is worthwhile to look for an alternative to these conventional methods by using medicinal plants or phytotherapy. In fact, many developing countries including China use herbal medicines which have gained popularity in Europe and are becoming increasingly in the United States as well. As far as urolithiasis is concerned, several herbal treatments seem to cure lithiasis patients. Nevertheless, the effectiveness and the mechanism by which these plants work has not been fully undertaken by using scientific and objective methods. Therefore, it is highly recommended to explore new drugs coming from medicinal plants to treat and prevent the formation of kidney stones. Ideally, conventional and phytotherapy should supplement one another and have all the need available for lithiasis patients.

### 2. INTRODUCTION

Urolithiasis, referred to the formation of a stone in urinary tract, is one among the diseases that afflicted humans since antiquity. Despite tremendous advances

accomplished in understanding the mechanisms governing the formation of such concretion, the disease remains an enigma since several factors intervene and interfere each other. As many forms of mineralization, urolithogenesis encompasses several physico-chemical steps which occur either sequentially or concurrently that start with supersaturation, then nucleation, growth, and aggregation (1, 2). Of course, based on their size, aggregated particles can be attached and retained within urinary tubule epithelium constituting an additional step in calculogenesis. According to clinical and epidemiological studies, calcium oxalate (CaOx) followed by calcium phosphate are the most frequently encountered crystalline components found in analyzed stones (3). Most stones do not contain one single crystal phase but rather a mixture of several different crystal phases. This leads to wonder which phase was initiated the crystallization process. Whatever the answer will be, the main question is why certain people form urinary calculi and some other do not?

It is well known that kidneys reabsorb water and contribute to the concentration of different solutes that might crystallize and precipitate. Therefore, any subject is susceptible to form a calculi. Fortunately, this is mostly not the case and only few persons are predisposed to form such concretion. The most simple explanation for the occurrence of kidney stones would be that the urine of stone formers is supersaturated with stone minerals, which consequently precipitate in their urine. Equally, healthy persons have a supersaturated urine as well and occasionally pass crystals in their urine (4). However, recurrent stone formers tend to excrete such crystals in greater quantities and clustered into large particles than those observed in healthy subjects (5). This difference is due to the presence in the urine of healthy persons of so called urinary inhibitors that alter the process of crystallization and consequently prevent the

development of a stone (6). Thus, attempts have been made to characterize these inhibitors with an objective to find a difference between healthy and stone formers that might lead to the formulation of a treatment. Among the earliest reported inhibitors were pyrophosphate and citrate (7). However, it was found later that the majority of inhibitory activity is supported by macromolecules such as ribonucleic acids and peptides. Due to the progress made in protein chemistry and molecular biology during the last two decades, a substantial amount of information is currently available about the inhibitory macromolecules including their purification, identification as well as their synthesis and biological activity (6, 8). According to several of these studies, urinary macromolecules can bind onto the surface of crystals preventing and reducing especially their growth and aggregation. The same molecules purified from the urine of stone formers showed less inhibitory activity (9-11). Structural defects or post-translation modifications may occur and explain the decrease of inhibitory activity of these macromolecules. So, at this level we can wonder if these inhibitory substances can be used as therapeutic agents to treat and prevent kidney stone formation?

### 3. TREATMENT OF KIDNEY STONES

Patients who have produced one or more stones are susceptible to become recurrent stone formers. It is then highly desirable to provide an efficient stone preventive treatment. A stone can form only when urine is supersaturated with respect to its constituents such as CaOx, the most abundant element in analyzed kidney stones. To reduce the propensity of salts to crystallize in the urine, patients with kidney stones, regardless their composition, should take some measures including dietary restrictions and increasing fluid intake. Indeed, it was observed that hydration aiming to increase urinary output greater than 2 liters is effective to reduce stone formation (12). The major guidelines for dietary modifications include restriction of salts, avoidance of animal protein-rich diet, restriction of food with high oxalate content, and moderate intake of dietary calcium (13). When these conservative methods are not sufficient to prevent stone formation, at this level, drug therapy appears to be suitable method of choice. Most drugs are generally used to restore metabolic abnormalities once they are detected and well established among them hypercalciuria, hypocitraturia, hyperuricosuria, and others. The mechanism of action of these drugs are mostly based on the chelation of ions such as calcium and magnesium or inhibition of absorption and synthesis of metabolites. Some of these drugs are briefly described below.

#### 3.1. Inhibitors

##### 3.1.1. Low molecular weight inhibitors

Pyrophosphate was the first molecule identified and has been the objective of numerous studies to determine its role in urinary crystallization. Indeed, it was postulated that it is mainly an inhibitor of nucleation of calcium phosphate and it inhibits up to 50% of hydroxyapatite crystal growth. Oral supplementation with orthophosphate aiming to increase urinary pyrophosphate was suggested as a therapeutic agent. However, its

beneficial use was very limited and even ineffective. Diphosphonates molecules, structural analogues of pyrophosphate such as ethane-1-hydroxy-1, 1-diphosphonate (EHDP), have been also tested since they showed more inhibitory activity towards calcium oxalate crystals. Unfortunately, its effective dose needed to inhibit crystallization appeared to be toxic which compromised its use in therapy (14).

Another effective prophylactic drugs is citrate, a calcium complexing agent. Citrate is one of the most important inhibitors of calcium oxalate stone formation endogenously found in urine. Studies estimate that 19-63% of individuals with calcium nephrolithiasis have hypocitraturia as a contributing cause. In fact, citrate chelates calcium and forms a soluble solute that reduces the level of free calcium ions that might be available to form complexes with oxalate and phosphate. Oral administration of citrate indirectly increases its excretion in the urine. Therefore, potassium citrate is indicated for the prevention of recurrent stone formation due to distal renal tubular acidosis, thiazide-induced hypocitraturia (15), hyperuricosuric calcium nephrolithiasis (16), idiopathic hypercitraturia (17), and uric lithiasis (18). In the above conditions, the efficacy of potassium citrate was demonstrated in both nonrandomized and randomized trials (19). Unfortunately, the treatment by using potassium citrate has serious potential drawbacks including the development of hyperkalemia in patients with type IV renal tubular acidosis, or those who have renal impairment. Another potential complication is gastric bleeding, intestinal obstruction, diarrhea, nausea, burning that may occur during the use of liquid potassium citrate. Furthermore, some concern has been raised that long term potassium citrate therapy may cause aluminum toxicity. Indeed, citrate from potassium citrate could form a soluble complex with aluminum contained in food (20). Several aluminum toxicity has been reported following ingestion of soluble citrate with aluminum containing gels in patients with end-stage renal disease (21).

Similarly to citrate, magnesium can bind and form soluble complexes with oxalate reducing in this way the supersaturation and decrease the oxalate ion concentration susceptible to react with calcium and precipitate. Numerous studies *in vitro* demonstrated that magnesium is a potent inhibitor of calcium phosphate CaOx crystallization inhibiting especially crystal nucleation and growth (22, 23). However, its actual role as an inhibitor in urine remains controversial since the results of studies conducted in animals are discordant. Indeed, magnesium oxide, tested at 200 mg/100 g of rat chow showed no significant changes occurred on CaOx nephrolithic rats (24). However, when this dose is increased to 500 mg, magnesium oxide prevented the deposition of CaOx crystals into rat kidneys (25). Similarly, the results of clinical studies are conflicting too since it was shown that magnesium has proved to be beneficial in preventing and reducing stone formation, but not confirmed in other studies (26-29). Overall, the use of magnesium in therapy of lithiasis patients seemed to be limited. However, its use

in some particular cases of hypomagnesiuria is justified (30).

### 3.1.2. High molecular weight inhibitors

According to the results conducted *in vitro* showed that ribonucleic acid (RNA) were the most active macromolecules tested inhibiting CaOx crystal growth and aggregation. This important effect on crystallization seemed to be due to the presence of numerous negative charges on the surface of these macromolecules. However, when these substances were tested in presence of the urine, their inhibitory activity decreased dramatically. It appeared that RNAase present in the urine contributed to hydrolysis of RNA and they limited their inhibitory activity. Consequently, the role of RNA on the prevention of kidney stone formation appeared to be restricted.

Glycosaminoglycans (GAGs) are polymers constituted with disaccharide units. The main GAGs in urine are chondroitin sulfate representing 60% followed by heparan and keratan sulfate representing 15% for each. Numerous studies interested in quantification of urinary GAGs were not conclusive since some of these studies showed that lithiasis patients excreted less GAGs than normals but not confirmed in others. The most interest given to GAGs is their ability to inhibit CaOx crystallization. Several experimental models *in vitro* have showed that heparan sulfate is the most powerful inhibitor followed by chondroitin sulfate. This action seemed to be due to their adsorption onto the surface of crystals. Such property prompted many investigators to use natural and synthetic GAGs, sodium pentosan sulfate for example, as therapeutic agent in the treatment of urolithiasis (31). Even these attempts have shown some beneficial effect, side effects restricted the use of GAGs especially for long term treatment.

### 3.2. Other drugs

Based on their hypercalciuric action, thiazides are used to treat hypercalciuric nephrolithiasis patients. Indeed, it was reported that thiazides especially hydrochlorothiazide reduced significantly the formation of stones when compared to a placebo group. Nevertheless, thiazide therapy is limited by side effects like fatigue, malaise, impotence, and constipation (32). In addition, there are development of hypokalemia, hyperuricemia, and hyperuricosuria. Some studies showed that the long term treatment with thiazides may be limited since the urinary calcium returned to its initial level before the treatment (33).

Sodium cellulose phosphate (SCP) is used to restore normal calcium excretion by reducing intestinal calcium absorption. Numerous investigations have shown its efficacy by the reduction of stone formation (34). However, this treatment is associated with two potential complications that may compromise therapy. The SCP may induce hypermagnesiuria leading to increase saturation of CaOx due to reduced complexation of urinary oxalate by magnesium (35). Also, the reduction of intraluminal calcium available for complexation with oxalate leads to an

increase in the pool of free oxalate and then contributing to hyperoxaluria.

In certain circumstances associated with dietary changes, urine may become supersaturated with respect to monosodium urate leading to hyperuricosuria. This agent might induce heterogeneous nucleation of CaOx and promote indirectly CaOx crystallization by precipitation of urinary inhibitors (36). Dietary restriction may suffice to reduce monosodium urate excretion in case of mild hyperuricosuria. However, in most cases, this conservative method is inadequate and drug treatment appears to be most appropriate. Among the drugs available are allopurinol accompanied by alkalization of urine and augmentation of diuresis. Nevertheless, some side effects could appear during the treatment such as skin rash and lead to its discontinuation. In case of high dose, allopurinol may conduct to the formation of xanthine and oxypurinol calculi (37).

It is important to outline that in addition to the most known drugs reviewed briefly in the section above, we have to add that some drugs rather promote the formation of urinary stones. Indeed, among the earliest observations of the existence of drug related stones came from the use of sulfa drugs. In addition to urinary pH, dehydration seems to accentuate the precipitation of these drugs.

In certain drug programs, triamterene is used to prevent urinary potassium loss in combination with thiazides. However, the intake of triamterene resulted in formation of stones containing this drug (38).

Recently, it was shown that administration of indinavir, a protease inhibitor used to treat patients with AIDS, led to the formation of urinary stones.

To all these drugs, other medications have been detected in urinary stones (39). This urges all urologists to take this phenomena into consideration when there are treating their lithiasis patients.

### 3.3. Extracorporeal shock wave lithotripsy (ESWL)

In the last two decades, the treatment of urolithiasis has changed dramatically. Currently, open renal surgery for nephrolithiasis is unusual and rarely performed. Lastly, the introduction of ESWL has revolutionized the urologic practices and become nearly a standard procedure for the elimination of kidney stones (40). However, compelling data showed that exposure to ESWL may cause acute renal injury, a decrease in renal function, and an increase in stone recurrence (41, 42). Furthermore, traumatizing effect of shock waves, persistent residual stone fragments after ESWL, and possibility of infection represent serious problems to be taken into consideration in the treatment of stones. Thus, medical therapy is needed even to promote and facilitate the elimination of stone fragments after ESWL.

After all, treatment and prevention of kidney stones has considerably evolved during the last two decades by combination of different methods including dietary procedures, ESWL, and medicaments but as mentioned above, side effects of these methods and persistent of recurrence remain as problems to overcome. Thus, an alternative to these conventional methods is highly recommended. So, why not phytotherapy?

### 3.4. Phytotherapy

#### 3.4.1. Social and economic impact

Only a decade ago, alternative medicine in America was still a distinctly counterculture phenomenon. It has now become an established presence in mainstream culture. In fact, a national survey was conducted in 1990 in US about the use of unconventional therapies for health problems (43). The survey recovered 1539 adults by telephone interview. One of three (34%) of respondents reported using at least one unconventional therapy in the past year and 10.2% of them have seen a providers for unconventional therapy. In 1998, this percentage has increased to 15.1% (44). The frequency of use such therapy varied some what among socio-demographic groups with the highest use reported by non black persons who had relatively more education and higher incomes. The majority used unconventional therapy for chronic and serious conditions. The interesting thing in this study is the revelation that 70% of the respondents who used unconventional therapy did not inform their medical doctor that they had done so. Clearly, the use of plant products as medicines is widespread and growing. In 1996, Brevoort estimated the size of the 1994 US herbal market at \$1.6 billion (45). By 1998, her estimate had increased to \$3.9 billion. A 1996 survey by prevention magazine and ABC News reported that 1 in 3 Americans use herbal medicines, estimating the size of the annual herbal market at \$3.2 billion (46). Several national polls in 1997 and 1998 corroborated these estimates, reporting that 32% to 37% of Americans use medicinal botanicals in a given year.

One of the among unconventional therapy that we will focus on is phytotherapy or the use of plants in the treatment of diseases especially kidney stone formation. Indeed, herbal medicine is as ancient as the history of man kind. From the every beginning, herbal treatment has been a favorite tool of naturopathically inspired practitioners. Of course, conventional medicine has also derived many of its drugs from plants sources. According to the World Health Organization, approximately 75% of the global population, most of the developing world, depends on botanical medicines for their basic healthcare needs (47). Substances first isolated from plants account for approximately 25% of the western pharmacopoeia, with another 25% derived from modification of chemicals first found in natural products (48).

#### 3.4.2. Scientific evidences

As far as urolithiasis is concerned, acupuncture, herbal medicine, natural products, and homeopathy have been used to treat and/or to alleviate symptoms of lithiasic patients. Concerning herbal medicines, there is a large number of species described in many pharmacopoeia of

several countries in the world as remedies for urolithiasis. However, few investigators have devoted their efforts to study these plants by using objective and scientific methods. Such studies are needed to understand the mechanism by which these plants exert their effects and identify their active principles. In this regard, roots of rhubarb, a Chinese medicine plant, has been evaluated for its therapeutic potential to treat experimental chronic renal failure conducted in rats. The results showed some beneficial effects of the plant in terms of reduction of proteinuria and severity of glomerulosclerosis as well as the diminution of urea concentration (49, 50).

The efficacy of rice-bran therapy was evaluated in patients with idiopathic hypercalciuria (51). During the treatment, it was noticed a reduction of urinary calcium excretion. These results were confirmed experimentally and clinically (52). In another study conducted in 164 hypercalciuric patients with calcium-containing urinary stones, the frequency of stone episodes was reduced dramatically from 0.462 to 0.101 per patient per year (53). Urinary calcium excretion was considerably reduced while urinary phosphate and oxalate were slightly increased. Interestingly, the treatment was well tolerated and no side effects were observed even it was conducted for up to 43 months for certain patients.

Grases and colleagues have studied the efficacy of some medicinal plants such as *Rosa canina*, *Zea mays*, and *Herniaria hirsuta* on the urinary risk factors of calcium oxalate (54-56). Globally, except some little effect on calciuria and citraturia, no significant changes have been observed during the treatment on urinary chemistries. However, the important findings is that beneficial effect of these plants depends on diet.

To ascertain the beneficial effect of banana stem extract on urinary risk factors, a prospective study showed that the plant extract reduced significantly urinary oxalate in experimentally hyperoxaluric rats. Such effect could be beneficial in the treatment of patients with hyperoxaluria urolithiasis.

Another Chinese medicinal plant that has attracted more attention is Kampou medicine known to be used in the treatment of various disease for hundreds of years. It had been also used for prevention and treatment of urinary calculus. An experimental study suggested a direct inhibitory effect of Kampou extracts of calcium oxalate crystallization *in vitro* and *in vivo* (57). In this study, two species from Kampou, *Takusya* (*Alisma orientale*) and *Kagosou* (*Prunella vulgaris*), were employed to evaluate their stone prophylactic effect in an animal model. The results showed significant stone prophylaxis of *Takusya* while *Kagosou* did not. In the same study, Chorey-to which is a Chinese medicine that contains 5 Kampou plants including *Takusya*, has been evaluated *in vivo*. The low dose of this preparation exhibited apparent anti-stone effect despite the disadvantage of decreasing citrate excretion. *Takusya* had been also used to examine the inhibitory effect of the formation of calcium oxalate renal stones



**Figure 1.** Moroccan herbalist shop. Medicinal plants are collected, cleaned, and packed with a label indicating their name, doses, and contra-indication

induced by ethylene glycol and vitamin D3 in rats as well as on osteopontin expression that is identified as an important constituent of stone matrix (58). The rate of renal stone formation is lower in the group receiving *Takusya* extracts than in the control group. The expression of osteopontin in the rat group receiving the plant was smaller than in stone group. This finding suggests that *Kampou* medicine action include decreasing on calcium oxalate aggregation and growth as well as proliferation.

In Brazil, *Phyllanthus niruri* has been used to treat several pathological conditions (59). The plant has been called "break stone" because it has been used for generations as an effective product to eliminate gallstones as well as kidney stones. Such observation has been confirmed in rat model of urolithiasis induced by the introduction of CaOx seed into the bladder (60). Its effect was noticed particularly on crystal growth. The effect seemed to be independent of changes in the urinary excretion of citrate and magnesium but might be related to the higher incorporation of GAGs into calculi. The plant has been the subject of many phytochemical and pharmacological investigation in which different classes of compounds have been identified like alkaloids, flavonoids, lactones, steroids, terpenoids, lignans, and tannins. Some researchers have demonstrated an antispasmodic and an analgesic activities in *Phyllanthus niruri* which could explain the popular use of the plant for kidney and bladder stones (61). The alkaloid extract demonstrated smooth muscle relaxation specific to the urinary and biliary tract which facilitates the expulsion of both kind of stones (62). Lastly, the effect of an aqueous extract of *Phyllanthus niruri* has been investigated *in vitro* on a model of CaOx crystal endocytosis by Madin-Darby canine kidney cells in culture. The extract exhibited a potent and effective non-concentration dependant inhibitory effect on CaOx crystal internalization (63).

The antiurolithiasic activity of aqueous extract obtained from *Costus spiralis*, another Brazilian plant used to treat urinary affections and for expelling urinary stones, has been tested on formation of calculi on CaOx crystals or zinc implants in the urinary bladder of rats (64). The oral treatment after 4 weeks resulted in the reduction of calculi growth. The effect was unrelated to increased of diuresis or to a change of the muscarinic receptor affinity of the bladder smooth musculature.

In Morocco, as in many countries, a large number of patients use medicinal plants for treatment of urolithiasis (fig. 1). Indeed, the aerial parts of *Herniaria hirsuta* is used in folk medicine as a diuretic and for the treatment of kidney stones. We conducted a study to evaluate its effectiveness on CaOx crystallization *in vitro* (65). Our major findings are that, in the first hand, herb extract from *Herniaria hirsuta* considerably promoted the formation of CaOx crystals in whole urine by increasing their number but their size decreased inversely in a dose manner. Therefore, this property of the herb extract may be advantageous in preventing urinary stone formation by excreting small particles out off the kidney and reducing their chance to be retained in urinary tract. Furthermore, the presence of herb extract favored the formation of calcium oxalate dihydrate (COD) crystals rather than calcium oxalate monohydrate (COM) particles. We hypothesized that herb extract may contain substances that inhibit the growth of COM crystals. As far as urolithiasis is concerned, this property of *Herniaria hirsuta* is very important in preventing kidney stone formation. Indeed, it was shown that COD crystals are thermodynamically less stable and less attached to epithelial cell surfaces than COM particles. Thereby, a crucial step in kidney stone genesis can be prevented. In the second hand, our data showed that herb extract may contain substances that efficiently inhibited CaOx crystal aggregation. The importance of this result reside in the fact that agglomeration of particles, which is considered to be a crucial step in urinary stones formation, can be prevented. More recently, we evaluated the effectiveness of herb extract obtained from *Herniaria hirsuta* as a preventive and/or curative agent on nephrolithic rats (unpublished data). The results showed that for both protocols, preventive or curative, crystalluria in non treated rats was constantly predominated by big COM crystals and the presence of some COD crystals. However, in treated rats, crystalluria was characterized by the presence of large amount of small COD crystals and few numbers of COM crystals. According to these observations we postulated that the plant extract modulates the crystallization by inhibiting the formation of COM crystals and promotes the formation of small COD crystals that can be excreted easily from urinary tract. Histological slides showed clearly that the plant has a considerable antilithiasic effect. This effect was very important for rats belonging to curative protocol. Therefore, we can suggest that plant extract of *Herniaria hirsuta* is efficient to eliminate the pre-existing stones than to prevent them. It is probable that the plant has substances that can prevent the attachment of crystals onto cell membranes in urinary tract. Finally, the biological test of some methanolic fractions obtained from the plant may suggest the presence of an active principal which has the ability to inhibit the formation of COM crystals and promote the formation of COD crystals. Such effects have been seen when the total aqueous extract has been studied *in vivo*.

#### 4. CONCLUDING REMARKS AND PERSPECTIVE

It is well established that urolithiasis is characterized by its high recurrence if patients are not

treated appropriately. Several treatment programs include the use of various drugs that have shown their efficacy in eliminating or at least decreasing the incidence of stone recurrence. The introduction of ESWL has dramatically improved the surgical management of patients with kidney stones and open surgery is rarely performed. In spite of all advances made so far, treatment failure occurs. Therefore, efforts are needed to assess medical therapy better and also to develop new agents that can be used either alone or in combination to prevent stone formation efficiently in lithiasis patients. Accordingly, we believe that the rational investigation and incorporation of some botanical medicines may turn out to cause little harm and, hopefully, significant benefit since herbal medicines are widely used and therefore deserve to be studied. Thus, further research is needed to identify active principles from medicinal plants, to assess their dosage and quality control, and investigate their interactions and adverse effects. Now, standardized herbal extracts are popular in Europe and becoming increasingly so in US as well. The intention of standardization is to overcome the problem of variability in the potency of raw plants. Finally, it is highly recommended to encourage insurance companies to pay for alternative practitioners and urge urologists to include phytotherapy in their treatment programs. Ideally, conventional and alternative medicine should supplement one another. No approach to healing is so universally competent that it can address all health problems successfully. Patients need all the help that is available.

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