Safety and tolerability of *Phyllanthus niruri* (Chanca Piedra)

The safety and tolerability of *P. niruri* have been evaluated in the following studies.

Can Phyllanthus niruri Affect the Efficacy of Extracorporeal Shock Wave Lithotripsy for Renal Stones? A Randomized, Prospective, Long-Term Study

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Purpose: Phyllanthus niruri is a plant used in Brazilian folk medicine for the treatment of urolithiasis. We assessed the efficacy of P. niruri after extracorporeal shock wave lithotripsy for renal stones.

Materials and Methods: We prospectively evaluated 150 patients with renal stones that were as large as 25 mm and composed of calcium oxalate. All patients received 1 to 3 extracorporeal shock wave lithotripsy sessions by Dornier Lithotriptor S. After treatment 78 of 150 patients (52%) underwent therapy with Uriston®, a P. niruri extract (2 gm daily) for at least 3 months (group 1). Otherwise 72 of 150 patients (48%) were used as a control group (group 2). No significant difference in stone size between the 2 groups was found. Stone clearance was assessed after 30, 60, 90 and 180 days by abdominal x-ray and ultrasound scan.

Results: Stone-free rate (stone-free defined as the absence of any stone or residual fragments less than 3 mm) was 93.5% in group 1 and 83.3% in group 2 ($p = 0.48$) at the end point of the followup (180 days). For lower caliceal stones (56 patients) the stone-free rate was 93.7% in the treatment group and 70.8% in the control group ($p = 0.01$). Re-treatment need for group 1 was 39.7% and for group 2 it was 43.3% ($p = 0.2$). No side effects were recorded with extracorporeal shock wave lithotripsy or P. niruri therapy.

Conclusions: Regular self-administration of P. niruri after extracorporeal shock wave lithotripsy for renal stones results in an increased stone-free rate that appears statistically significant for lower caliceal location. Its efficacy and the absolute lack of side effects make this therapy suitable to improve overall outcomes after extracorporeal shock wave lithotripsy for lower pole stones.

Key Words: kidney calculi, lithotripsy

Extracorporeal shock wave lithotripsy represents a minimally invasive treatment for renal stones. The efficacy and safety of this procedure are well proven and demonstrated. Stone-free rates after ESWL® may vary according to stone size,[1] location[1–3] and the type of lithotriptor used.[4,5] Medical therapies may be used to avoid stone relapse, and these consist traditionally of citrate, potassium and magnesium, which act to correct the imbalance between the promoter and inhibitors of lithogenesis. Other therapies are used to dissolve stones. For many years litholytic agents such as Herniaria hirsuta, kampou extracts and other plants were a common way to treat urinary stones, especially in semi-arid zones and in countries with unreliable water sources.[6–8]

Phyllanthus niruri is a plant traditionally used in Brazilian folk medicine for the treatment of several pathological conditions, including urolithiasis. The plant may act as an inhibitor of crystal growth, because of a higher incorporation of glycosaminoglycans into the stone.[9] Uriston® consists of an extract from P. niruri labeled with specifics tannins. We assessed the efficacy of chronic therapy with Uriston® after ESWL® for renal stones composed of calcium oxalate.

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MATERIALS AND METHODS

From January 2003 to February 2005 we prospectively evaluated 150 patients with renal stones thought to be composed of calcium oxalate. Subjects with urinary tract infections, pregnant women or patients who already underwent renal surgery were excluded from the study. Stones were investigated through abdominal x-ray, ultrasound and excretory urogram. Patients were submitted to 1 to 3 session of ESWL® with the use of Dornier Lithotriptor S.

After ESWL® patients were randomly divided in 2 groups. Group 1 consisted of 78 patients who received an adjunctive treatment with oral medical therapy, and group 2 consisted of 72 patients who did not receive any therapy and served as a control group. The medical therapy of group 1 consisted of 2 gm per day of Uriston®, an extract from P. niruri self-administered once a day for a minimum of 90 days. Both groups were allowed to use symptomatic therapy with ketoprofen on demand and were asked to drink a minimum of 2 liters of water daily. Stone clearance was assessed after 30, 60, 90 and 180 days by abdominal x-ray and ultrasound scan. A stone-free condition was defined as the complete absence of any stone or the presence of residual fragments smaller than 3 mm.

Sampled data were inserted in a database and statistically analyzed with the help of SPSS® 8.0 version for Windows. A complete descriptive analysis of all available vari-

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TABLE 1. *Patient and stone characteristics*

	Group 1	Group 2	p Value
Mean pt age (range)	50 (25–78)	48 (24–73)	
Mean mm stone size (range)	12.2 (5–25)	11.5 (5–20)	
No. stone location:			
Upper caliceal	9	14	0.14
Middle caliceal	16	10	0.22
Lower caliceal	32	24	0.10
Pelvis	21	24	0.68

ables was performed. Statistical analysis was performed with student's t test, the Mann-Whitney U test, the chi-square test and 2-tailed Fisher's exact test. A significance level of 0.05 was chosen for all the tests.

RESULTS

All patients completed the study. Group 1 consisted of 42 men and 36 women (average age 50 years, range 25 to 78), and group 2 consisted of 38 men and 34 women (average age 48 years, range 24 to 73). The average stone size was 12.2 mm (range 5 to 25) for group 1 and 11.5 mm (range 5 to 20) for group 2, with no statistically significant difference between the 2 groups. Stone location in the kidney is reported in table 1. A Double-J® stent was placed before ESWL® in each case in which the stone size was larger than 20 mm. The average number of shock waves per session was 3,000 for both groups (range 2,400 to 3,500). Ultrasound and x-ray were used for focusing on the stone.

Stone-free condition with residual fragments less than 3 mm occurred in 73 (93.5%) of 78 patients in group 1 and in 60 (83.3%) of 72 patients in group 2 at the end point ($p = 0.48$). Stone-free condition without residual fragments occurred in 69 (88.5%) of 78 patients in group 1 and in 55 (76.4%) of 72 patients in group 2 ($p = 0.08$).

Table 2 presents the stone-free rates for different stone locations. Outcomes stratified by stone size and by different steps of followup (30, 60, 90 and 180 days after ESWL®) are reported in table 3. Regarding the stone-free patients, 29 of 73 in group 1 (39.7%) and 26 of 60 in group 2 (43.3%) underwent ESWL® re-treatment ($p = 0.2$). All the collected stones turned out to have a predominantly calcium oxalate composition (greater than 70%).

Medical therapy with Uriston® for group 1 lasted from 95 to 200 days (mean 134). No side effects were noticed during the treatment, neither with ESWL® nor with P. niruri intake. Patients who were not stone-free after 180 days (5 in group 1 and 12 in group 2) were successfully treated with percutaneous lithotripsy.

TABLE 2. *Outcomes stratified by stone location*

	% Group 1 Stone-Free	% Group 2 Stone-Free	p Value
With residual fragments less than 3 mm:			
Overall	93.5	83.3	0.10
Upper caliceal	100	92.8	0.06
Middle caliceal	93.7	90	0.54
Lower caliceal	93.7	70.8	<0.001
Pelvis	90.4	87.5	0.75
Without residual fragments:			
Overall	88.5	76.4	0.08
Upper caliceal	88.8	85.7	0.63
Middle caliceal	87.5	80.0	0.86
Lower caliceal	90.6	62.5	0.03
Pelvis	85.7	83.3	0.85

TABLE 3. *Outcomes stratified by stone size and followup*

	% Group 1 Stone-Free	% Group 2 Stone-Free	p Value
Stone size (mm):			
Less than 10	97.2	84.6	0.02
Greater than 11	90.4	82.6	0.24
Days followup:			
30	54	18.8	0.02
60	69.3	35.2	0.03
90	74.3	64.2	0.38
180	93.5	83.3	0.48

DISCUSSION

ESWL® represents a minimally invasive treatment for renal stones, and its efficacy and safety have improved accordingly with technological progress.[4,5,10] Nevertheless, outcomes of ESWL® may be affected by a number of features connected to both stone and patient characteristics. It is well known that stone size,[1] location[1–3] and composition[11] influence the clearance of residual fragments while a high body mass index compromises the results of stone focusing.[12]

As the technology has improved, some authors have reported outcomes of ESWL® with regard to the type of lithotriptor used. Matin et al found a comparable efficiency quotient between electrohydraulic and electromagnetic units.[4] Sheir et al, with a prospective, randomized comparative study, recently reported an overall stone-free rate of 88.5% and 82.4% for Dornier Lithotriptor S and Dornier MFL 5000, respectively.[5] Other studies investigated ESWL® results based on the location of the stones. Obek et al described an overall stone-free rate of 66% with a Lithostar® lithotriptor with 63%, 73% and 71% stone clearance for lower, middle and upper isolated caliceal stones, respectively.[13]

Lower pole stones still represent a difficult problem due to the reduced discharge of the fragments and their consequent recrystallization. The cause may be based on morphological features of the kidney. Elbahnasy et al described the 3 major radiographic characteristics of the lower pole that influence ESWL® outcomes as infundibulopelvic angle, infundibular length and width.[3] Other clinical studies of 10 to 20 mm lower caliceal stones found stone-free rates varying from 37% to 79.2%.[14,15]

Supportive medical therapy to improve ESWL® results has been attempted in the past by using potassium or magnesium citrates. Cicerello et al suggested that citrate reduces growth or agglomeration, increasing the clearance rate of calcium oxalate.[16] Soygur et al investigated the effect of potassium citrate therapy on the stone recurrence rate and the percentage of residual fragments after ESWL®. In the residual fragment group treated patients had a significantly greater remission rate compared to untreated patients (44.5 vs 12.5%), and no recurrences were noticed at 12 months in the stone-free group following potassium citrate therapy.[17]

In this study we evaluated the efficacy of Uriston®, an extract from P. niruri, after shock wave lithotripsy for renal stones. P. niruri is a plant belonging to the Euphorbiaceae family with a worldwide distribution. It is traditionally used in Brazilian folk medicine in the treatment of urolithiasis. Several authors have investigated its mechanism of action. In

1998 Campos and Schor described the powerful inhibitory effect of P. niruri on CaOx crystal adhesion and suggested that P. niruri intake may reduce urinary calcium in patients with hypercalciuria.[18,19] Barros et al confirmed the inhibition on CaOx crystal growth and aggregation with an in vitro aqueous extract from P. niruri.[20]

Freitas et al suggested that this effect was related to a higher incorporation of glycosaminoglycans into the stone, independently from urinary excretion of citrate and magnesium.[9] In fact, the calculi from a P. niruri treated group had a higher content of GAGs, suggesting that P. niruri reduces the deposition of crystalline particles.

The actual role of GAGs in urolithiasis has been widely evaluated and discussed. GAGs and especially chondroitin sulfate bind to the growth sites of crystals and therefore stop their aggregation. The outcomes of our experience may support all these premises in that residual fragments due to ESWL® seem to have a lower aggregation and crystallization potential.

Complete stone clearance occurred in 93.5% of patients in the treated group but only in 83.3% of patients in the control group. Taking into consideration lower caliceal stones, 93.7% of Uriston® patients were stone-free at 180 days compared to 70.8% of patients in the nontreated group. Stone size ($p = 0.02$) and medical therapy ($p = 0.03$) were the main predictors of stone clearance.

P. niruri reduces the relative risk of ESWL® failure 10.3% overall and 33% for stones located in the inferior calix. Further studies are required to fully understand the role of P. niruri. Nevertheless, clinical outcomes with the use of P. niruri after ESWL® are remarkable as they show a statistically significant increase in ESWL® effectiveness.

CONCLUSIONS

Regular intake of P. niruri after ESWL® results in an increased overall stone-free rate, in a lower re-treatment percentage and in a faster stone clearance. Its efficacy is only evident for stones in the lower caliceal location, where it may act to prevent recrystallization of stone fragments and thus increase their clearance. The effectiveness of P. niruri together with the absolute lack of side effects make this therapy suitable for improving overall outcomes of shock wave lithotripsy for lower pole renal stones.

Abbreviations and Acronyms

CaOx	=	calcium oxalate
ESWL®	=	extracorporeal shock wave lithotripsy
GAG	=	glycosaminoglycans

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Review Article

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Phyllanthus niruri as a Promising Alternative Treatment for Nephrolithiasis

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ABSTRACT

In spite of considerable efforts to identify effective treatments for urolithiasis, this is a goal yet to be achieved. This review summarizes experimental and clinical data evaluating the effect of the plant Phyllanthus niruri, a plant with worldwide distribution, as a potential agent to prevent and/or to treat urolithiasis The review is based on data from the literature and on the results obtained by our group from either in vivo/in vitro experiments or clinical studies. Phyllanthus niruri has been shown to interfere with many stages of stone formation, reducing crystals aggregation, modifying their structure and composition as well as altering the interaction of the crystals with tubular cells leading to reduced subsequent endocytosis. The clinical beneficial effects of Phyllanthus niruri may be related to ureteral relaxation, helping to eliminate calculi or to clear fragments following lithotripsy, or also to a putative reduction of the excretion of urinary crystallization promoters such as calcium. No adverse renal, cardiovascular, neurological or toxic effects have been detected in either of these studies. Altogether, these studies suggest a preventive effect of Phyllanthus niruri in stone formation or elimination, but still longer-term randomized clinical trials are necessary to confirm its therapeutic properties.

Key words: *renal; lithiasis; treatment; clinical; Phyllanthus niruri*
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INTRODUCTION

Urinary stones affect 10-12% of the population in industrialized countries. Their incidence has been increasing over the last years and the age of onset is decreasing. In addition, the recurrence rate is high, more than 50% after 10 years (1,2). Genetic, metabolic, environmental and dietetic factors are involved in the pathogenesis of urolithiasis, all of them propitiating the crystallization of salts inside the renal tubules, further retention and growing to form a stone (3). Given that urine is normally a supersaturated solution, crystalluria is often observed in normal individuals, but if crystals remain apart from each other, they are washed away by urine flow. However, under certain circumstances they bind each other due to chemical and electrical forces triggering the process of aggregation. The crystals or aggregates then attach to the epithelium which allow them to grow further and form the stone (4). Moreover, calcium oxalate (CaOx) crystals, the main constituent of human urinary calculi, may adhere in a specific manner to the plasma membrane of epithelial cells and this process is followed by endocytosis of the crystals resulting in cell damage or death (5,6). Damaged cells exhibit a proliferative response, increase the synthesis of fibrogenic substances promoting additional stimulus for crystal growth (7,8). In addition, dead cells detach

from the basement membrane and the cellular debris will adhere to other crystals resulting in a stone nidus. Thus, the cellular pathways involved in endocytosis of CaOx crystals can constitute potential targets for drugs designed for the prophylaxis and/or treatment of urolithiasis. Different substances have been described as modulators of adhesion and/or endocytosis processes (9-11) but none of them seem to be suitable for clinical use. On the other hand, alternative treatments such as the traditional herbal treatments can compliment pharmacotherapies for prevention and/or treatment of urolithiasis with less expense and perhaps fewer side effects, as reviewed by Miyaoka and Monga (12).

We have been evaluating the effects Phyllanthus niruri on several stages of stone formation as well as its potential therapeutic potential in lithiasic patients. Experimental and clinical studies performed by our group and by others have produced interesting and hopeful data concerning the potential therapeutic use of Phyllanthus niruri to treat and/or to prevent stone formation. These data are summarized in this review.

PHYLLANTHUS NIRURI

Phyllanthus niruri, popularly known as "stone-breaker" ("quebra-pedras") is a plant belonging to the Euphorbiaceae family with a worldwide distribution and it is used in folk Brazilian medicine for patients with urolithiasis (13). More than 50 compounds were identified in the Phyllanthus niruri, including alkaloids, flavanoids, lignans and triterpenes (14). Among these substances, the triterpenes have been found to inhibit the cytotoxicity induced by calcium oxalate (15) as well as to reduce excretion of stone forming constituents (16) and the markers of crystal deposition in the kidneys (17). Moreover, methanol extract from the leaves of Phyllanthus niruri containing substances such as lignans and phyllanthin showed a uricosuric activity in hyperuricemic rats (18). According to Calixto et al. (19) alkaloids extracted from plants of the genus Phyllanthus present an antispasmodic activity leading to smooth muscle relaxation, mostly evidenced in the urinary tract, which would facilitate the elimination of urinary calculi. These data strongly suggest that Phyllanthus niruri may be a potential source of many substances with antilithiasic properties.

Interestingly, given that the maintenance of normal levels of calcium is critical to the function of many plants including plant rigidity, protection, detoxification (heavy metals or oxalic acid), ion balance and even light reflection (20), and because high cellular free calcium concentration may be dangerous for these organisms, higher plants (plants exhibiting a vascular system) developed a very efficient way to neutralize Ca+2 ions, by forming complexes with oxalate (21). Oxalate producing plants, which include many crop plants, accumulate oxalate and as much as 90% of the total calcium in the form of CaOx crystals. Curiously, as shown in Figure-1, refractive CaOx crystals seen in the leaves of Phyllanthus niruri are kept equidistant, do not aggregate hence not forming stones. Therefore, understanding the basic molecular strategies by which some plants are able to package CaOx crystals may provide insights into the potential utilization of these plants to prevent/treat urolithiasis (22).

IN VITRO STUDIES

The effect of the aqueous extract of Phyllanthus niruri on crystallization process of CaOx in human urine has also been investigated in a model of in vitro precipitation of CaOx in human urine (23). Barros et al. (24) observed that the pre-incubation of

***Figure 1** – CaOx crystals observed in Phyllanthus niruri leaves observed under light microscopy.*

human urine with Phyllanthus niruri did not inhibit the precipitation of CaOx particles and even more crystals were obtained in Phyllanthus niruri-containing urine, but the crystals were proportionally smaller than those in urine samples without Phyllanthus niruri. Moreover, they observed that after 24 hours, the precipitated crystals formed large agglomerates in untreated urine, but the crystals remained dispersed in urine with Phyllanthus niruri (Figure-2). The authors concluded that Phyllanthus niruri did not decrease the number of crystals but induced a marked reduction of particle size and crystal aggregation. Similar results were obtained by Atmani E and Khan SR (25) employing a different plant species (Herniaria hirsute), which is used in folk medicine in the Mediterranean area for its diuretic properties and to treat kidney stones. Crystalluria is a common event observed even in non-stone forming individuals. CaOx crystals are found in urine under several forms including monohydrate (COM) and dihydrate (COD) forms. Unlike COD, which is predominantly found in normal individuals, COM crystals have higher capacity to aggregate and adhere, and is the main form excreted by the nephrolithiasis patients (26-28). In the model of in vitro precipitation of CaOx using human urine from healthy individuals, Phyllanthus niruri induced an increase in COD forms and reduced the amount of COM crystals, responsible for higher potential risk for stone formation.

Besides CaOx crystallization, it has been shown that the methanol extracts of Phyllanthus niruri showed an inhibitory activity of the enzyme xanthine oxidase in vitro (29) which was attributed to compounds such as flavonoids, polyphenols and tannins (30,31). Therefore, together with its uricosuric property (18), this enzymatic inhibition activity makes Phyllanthus niruri a potential antihyperuricemic agent.

STUDIES IN CULTURED CELLS

Campos and Schor (32) have demonstrated that Phyllanthus niruri exhibited a potent inhibitory effect on CaOx crystal adhesion and/or endocytosis

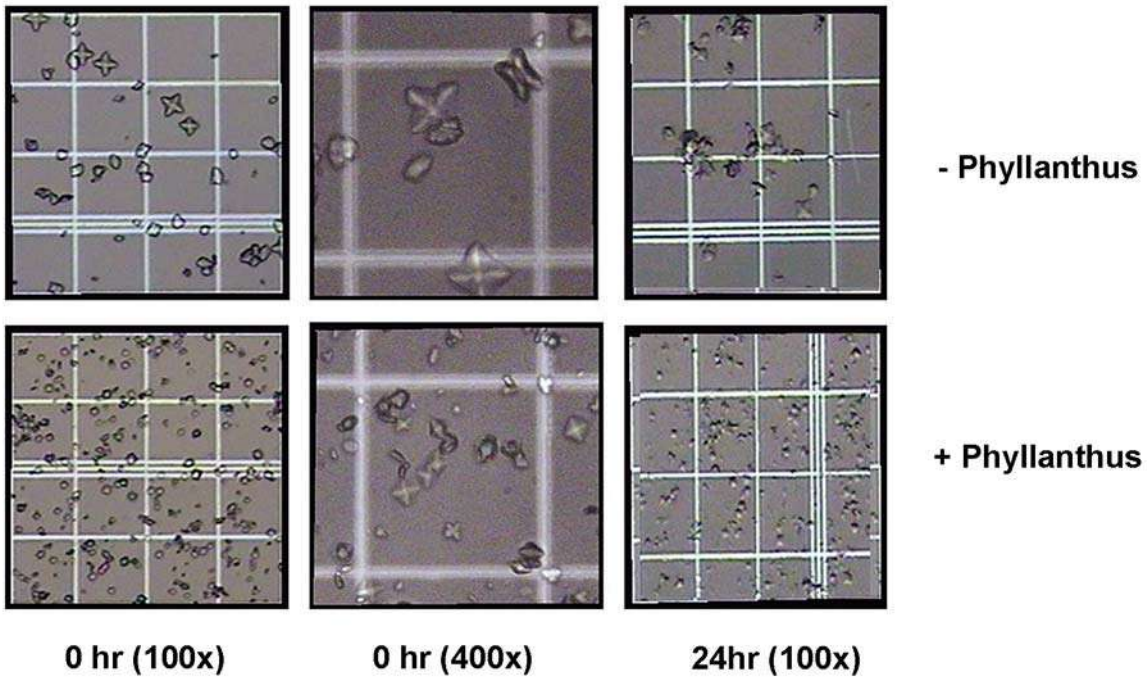

***Figure 2** – Light microscopy of CaOx crystals formed immediately (0 hr) and 24 hours after the addition of sodium oxalate solution in normal human urine and after in the absence and presence of Phyllanthus niruri. X100 and X400.*

by an immortalized cell line derived from canine kidney (MDCK cells) representative of the medullar collecting duct. This type of inhibitory effect occurred even when high doses (2.5 to 5-fold the upper limit in human urine) of CaOx have been employed and without causing cell toxicity.

EXPERIMENTAL MODELS IN RATS

The effect of Phyllanthus niruri has also been evaluated in experimental models of urolithiasis in rats, mainly those induced by implantation of a calcium oxalate (CaOx) crystal into the bladder (vesical foreign body method). This experimental model of urolithiasis is obtained with no significant metabolic or systemic alterations and the vesical CaOx seed acts as a supporting surface allowing organic and inorganic material to precipitate over the central nidus, mimicking a spontaneous calculus growth. It was initially shown that rats drinking Phyllanthus niruri tea ad libitum, presented decreased rate of stone growth (33). These effects occurred independently of any relevant modification in the urinary excretion of elements known to promote crystallization and stone formation, including calcium, oxalate, uric acid, pH, etc. In order to evaluate if the beneficial effect of Phyllanthus niruri could be mediated by modifications of the inhibitors of stone formation, such as citrate, magnesium and/or glycosaminoglycans, Freitas et al. (34) administered 1.25 mg/mL/day of Phyllanthus niruri for 42 days in rats with vesical CaOx seed. This chronic treatment induced a significant reduction in the calculi growth, in the absence of any modification in the volume diuresis or alterations in the urinary concentration of lithogenic elements including calcium and oxalate. Phyllanthus niruri administration did not modify the urinary excretion of citrate and magnesium, indicating that the putative antilithogenic effect of Phyllanthus niruri was not primarily mediated by modifications in these inhibitors. In contrast, it was observed that Phyllanthus niruri induced a decrease in the urinary excretion of glycosaminoglycans (GAGs) compared with lithiasic animals receiving water. In contrast, the content of GAGs was higher in calculi taken from treated animals suggesting that the inhibitory effect Phyllanthus niruri on crystal growth might have been related to higher incorporation of GAGs into the calculi. The adsorption of these macromolecules into the calculi lead to stones with a predominant intracrystalline amorphous organic matrix. Taken together, these results suggested that Phyllanthus niruri was able to prevent the aggregation of calcium oxalate to the pre-existent crystal without interfering with the incorporation of GAGs into organic matrix. Although the underlying mechanism remains to be clarified, some possible hypotheses can be raised: 1) a neutralization of negative charges of GAGs reduced the negative pole for progressive deposition of cations; 2) active components of the plant could have chelated and/or competed with calcium for binding sites on the crystal surface; 3) effects of Phyllanthus niruri itself on other proteins including Tamm-Horsfall protein, nephrocalcin, osteopontin, prothrombin fragment 1, etc, modulating crystallization, aggregation and calculi growth and 4) Phyllanthus niruri could reduce the crystal adhesion to the tubular epithelium. Essentially, these results suggest that Phyllanthus niruri could interfere with the calculi growth or prevent stone formation rather than dissolving pre-formed stones.

In order to better mimic what is observed in clinical practice, Barros et al. (35) using a vesical foreign body model in rats, compared the efficacy of Phyllanthus niruri treatment started concomitantly with CaOx seed implantation with the same treatment started 30 days after the seed implantation (when the vesical calculus was completely formed). As represented in Figure-3, the early treatment (Figure-3A) caused a significant inhibition in the calculi growth compared with non-treated animals (Figure-3B), as previously observed (34). In contrast, the treatment initiated after the stone formation, did not prevent the calculi to grow further neither propitiated calculi elimination; however it induced drastic changes in the shape and texture of the preformed calculi (Figure-3C). Stones taken from Phyllanthus niruri treated animals were more homogeneous and contained more compact surfaces (Figures 3D and 3E) in contrast to the spicule-shaped surface taken from untreated animals (Figure-3F). This result suggests that Phyllanthus niruri probably interferes with the biomineralization process, by promoting a different interaction between the crystal and the macromolecules of the organic matrix. Although Phyllanthus niruri had not

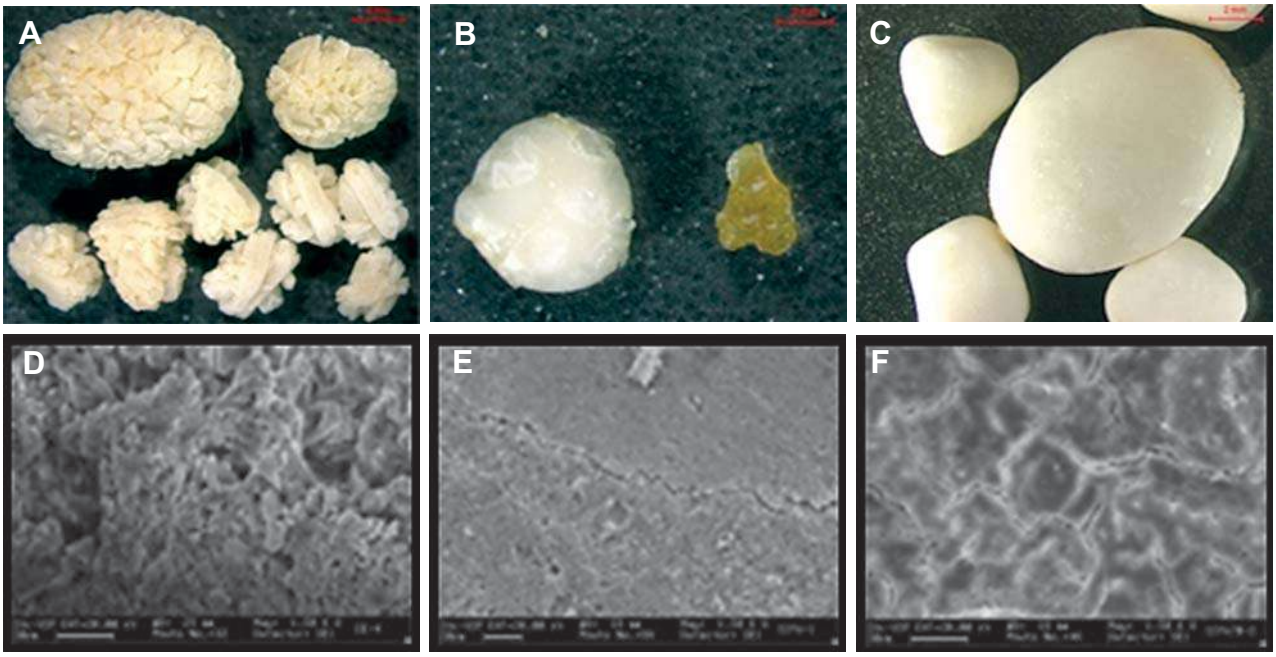

Figure 3 – *Upper and lower panels show the stereomicroscopy and scanning electronic microscopy respectively of the calculi taken from animals untreated (A and D), animals treated from the beginning (B and E) and from later treated animals (C and F).*

prevented the calculi growth, the treatment resulted in the formation of calculi with smoother surfaces, which could at least, contribute to less painful calculi voiding.

CLINICAL STUDIES

The initial study (33) addressing the effects of the Phyllanthus niruri administered in the form of tea did not demonstrate any clinical or biochemical adverse effects (cardiovascular, renal, hepatic or neurological) even at high dosage, with excellent tolerability in healthy volunteers. In addition, tea consumption in the same dose by nephrolithiasis patients for a period of 3 months, led to an apparent increased elimination of calculi compared to patients drinking placebo. These results were probably ascribed to the antispasmodic and relaxant effects of Phyllanthus niruri upon ureteral muscle, facilitating calculi voiding.

Subsequently, another study by Nishiura et al. (36), also in our Service, evaluated the effect of a lyophilized 2% aqueous extract of Phyllanthus niruri, in an additional series of 69 lithiasic patients in the form of 450 mg capsules (three times a day) compared with placebo (Chicorium sativum). In this short-term follow-up conducted during a three-months period, no significant differences in calculi voiding and/or pain relief between the groups taking Phyllanthus niruri or the placebo were detected. However, as patients were classified according to the presence of metabolic disturbance, a significant reduction in the mean urinary calcium excretion was observed only among hypercalciuric patients. The phytochemical and pharmacological properties of this plant have been accounted for the action of different substances such as Rutin, beta-amylin, beta-sitosterol, caffeic acid, geranin, quercetin, niruside and repandusinic acid. Although none of these compounds has been shown to have an effect on calciuria to date, such potential beneficial effect of Phyllanthus niruri for hypercalciuric patients needs to be further confirmed in longer-term studies involving a higher number of subjects.

Micali and coworkers (37) observed that patients submitted to extracorporeal shock wave lithotripsy and treated with Phyllanthus niruri during

Table 1 *– Summary of main findings.*

Studies	Main Findings	Reference
Models in vitro	Inhibition of CaOx crystal adhesion and/or endocytosis	32
	Reduction in crystals aggregation	24
	Increase in COD forms and reduced COM crystals	24
Models in vivo	Decreased rate of stone growth	34,35
	Increase intracrystalline amorphous organic matrix	34
	Changes in the shape and texture of the preformed calculi	35
Clinical	Increased calculi voiding	33
	Reduction in urinary calcium excretion in hypercalciuric patients	36
	Reduction in residual stone fragments after extracorporeal shock wave lithotripsy	37

COM = calcium oxalate monohydrate; COD = calcium oxalate dihydrate.

3 months presented lower incidence of residual stone fragments, mainly those in lower calyceal location compared with non-treated patients. According to these investigators, the efficacy and the lack of side effects of Phyllanthus help improve overall outcomes after extracorporeal shock wave lithotripsy and could be useful as either an alternative or an adjunctive therapy in the treatment of urolithiasis.

Table-1 summarizes the main findings in all studies. Given the experimental characteristic of these studies, except for the clinical ones (Grade of recommendation B), an exact level of evidence is not applicable.

CONCLUSION AND PERSPECTIVES

The experimental studies summarized here suggest that Phyllanthus niruri might interfere with important steps of the calculi formation including crystal aggregation and internalization by the tubular cells, crystal structure and composition. These properties of Phyllanthus niruri may constitute an important advantage in the prevention of lithiasis, inhibiting calculus growth and keeping the crystals dispersed in the urine, with their consequent easier elimination. Although clinical studies are less abundant, available data point to beneficial effects of Phyllanthus by inducing ureteral relaxation, interfering in the excretion of promoters of urinary crystallization such as calcium or helping to clear fragments following lithotripsy. It is important to consider however, that although it is clear that Phyllanthus niruri can interfere with many steps of the stone formation, longer-term clinical studies are necessary to define whether these effects can be translated into real clinical benefit to treat and/or prevent urolithiasis.

CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

The authors provide a nice review on the herb Phyllanthus niruri whose properties appear in fact to be promising assets in stone disease prevention and treatment. However, care must be taken to properly design future clinical studies in a way to provide reliable, consistent and reproducible data. As a major concern, I would point out the definition of accurate dosage and mode of intake. In a recent review on Chinese herbs used for managing stone disease, Miyaoka et al. (1) found several clinical trials demonstrating the likely benefits on stone prevention. However, the lack of standardization on dose and compounds between studies evaluating the same herbs made it extremely difficult to compare them and draw a sustainable conclusion. As a result, although used for hundreds of years with practical evidence of clinical benefits, Chinese herbs still strive to enter the armamentarium of stone therapy as a global consensus.

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