

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*

Int Braz J Urol. 2010; 36: 657-64

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 Ca²⁺ 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

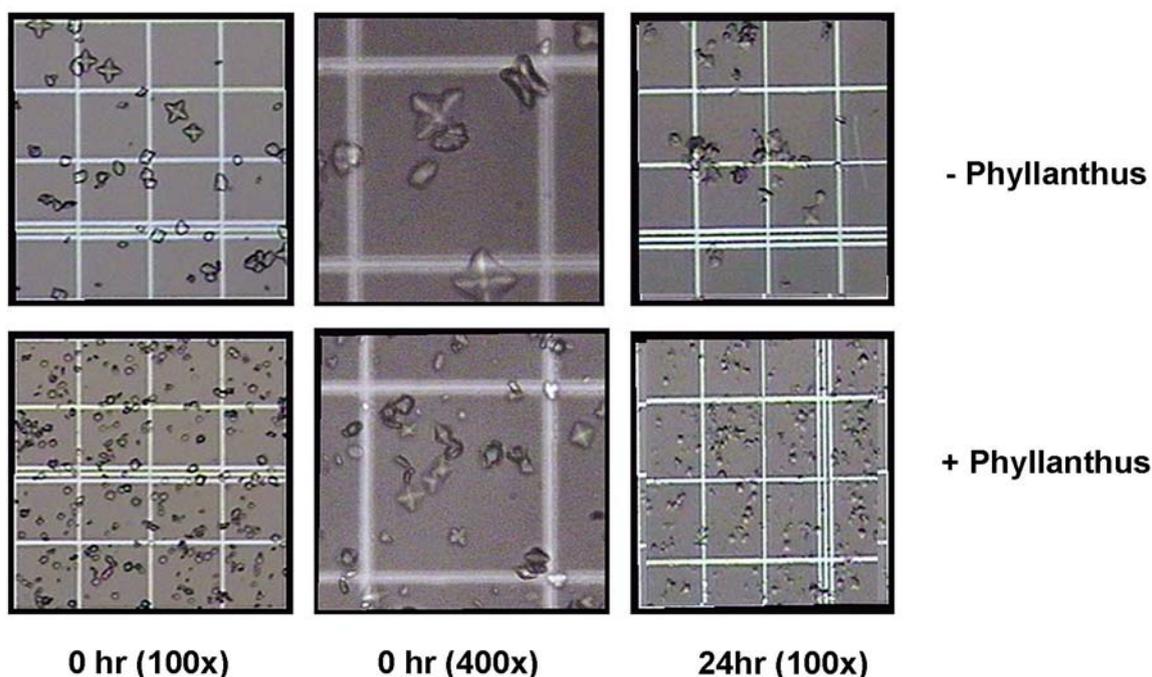


Figure 2 – Light microscopy of CaOx crystals formed immediately (0 hr) and 24 hours after the addition of sodium oxalate solution in normal human urine and after in the absence and presence of *Phyllanthus niruri*. X100 and X400.

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

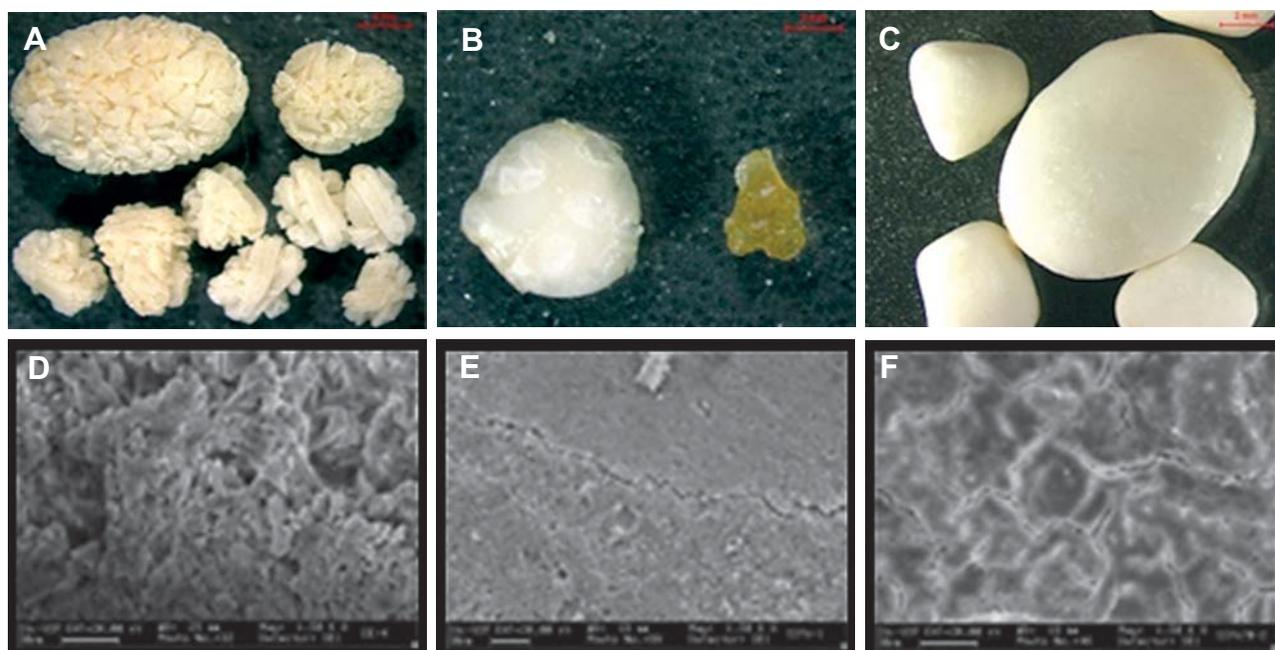


Figure 3 – Upper and lower panels show the stereomicroscopy and scanning electronic microscopy respectively of the calculi taken from animals untreated (A and D), animals treated from the beginning (B and E) and from later treated animals (C and F).

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, nirsidine 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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*Accepted after revision:
May 26, 2010*

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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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