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**PHYLLANTHUS NIRURI AND CHRYSANTHELLUM AMERICANUM IN  
ASSOCIATION WITH POTASSIUM AND MAGNESIUM CITRATES ARE ABLE TO  
PREVENT SYMPTOMATIC EPISODE IN PATIENTS AFFECTED BY RECURRENT  
URINARY STONES: A PROSPECTIVE STUDY**

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## **ABSTRACT**

### Objective

To evaluate the efficacy of a food supplement containing *Phyllanthus niruri* and *Chrysanthellum americanum* in association with potassium and magnesium citrates in the treatment and prophylaxis of symptomatic episode in patients affected by recurrent uncomplicated urinary stones.

### Materials and Methods

In this phase II clinical trial, all patients with history of recurrent uncomplicated urinary stones were enrolled. All patients received this food supplement, one capsule a day for 6 months, in an observational, prospective study in two referral institutions. Moreover, all patients were encouraged to make lifestyle changes. At the baseline, all patients underwent urologic visit with quality of life (QoL) questionnaires, serum chemistry, urinalysis and urinary tract ultrasound. After 6 months, all patients underwent urologic visit, urinalysis, instrumentation and QoL questionnaires evaluation. Main outcome measures were the rate of symptomatic episodes at the end of follow-up period.

### Results

From January 2018 to March 2019, 82 patients (mean age  $49.7 \pm 11.2$ ) completed the follow-up period and were analyzed. At the baseline, the average stone size was 7.8 mm and 23 patients showed asymptomatic bacteriuria (ABU). At the end of the follow-up period, the adherence to the treatment was high in 60 patients (73.1%). Twenty-seven patients out of 82 were stone-free (32.9%). Fifty patients showed lower stone dimensions (60.9%). The average stone size was 0.9 mm, with a significant reduction in comparison with the baseline ( $-6.7 \text{ mm} \pm 3 \text{ mm}$ ) ( $p < 0.001$ ). Forty-nine patients (59.7%) did not show any symptomatic episode with an improving in QoL ( $+0.4 \pm 0.1$ ) ( $p < 0.001$ ) in comparison with the baseline. Moreover, we report a significant reduction of patients with ABU between the baseline and the end of the follow-up evaluation (23 vs 3;  $p < 0.001$ ).

### Conclusions

In conclusion, this food supplement is able to improve quality of life in patients with urinary stones, reducing symptomatic episodes and the prevalence of ABU.

## INTRODUCTION

Urinary tract stones are one of the most common cause of urological visits, with a prevalence among urological patients of 1-15%<sup>1-2</sup>. The impact on everyday clinical practice is high, due to the high number of recurrences and due to the impact of symptoms on patients' quality of life<sup>2-3</sup>. The recurrence rate of urinary calculi is 50% within 10 years of the first episode<sup>3-4</sup>. Symptomatic recurrence episodes are associated with high direct and indirect costs (admission to emergency departments, instrumentations, drugs and working day lost). For these reasons, the prevention of symptomatic episodes due to urinary stones should be the first aim in the management of this kind of patients. Several authors recommended some diet interventions for reducing the risk of urinary stone formation and its recurrence but there is no conclusive consensus in the literature regarding the effectiveness of dietary interventions and recommendations about specific diets for patients with urinary calculi<sup>5</sup>. On the other hand, the use of medicinal plants and nutraceuticals have long been used worldwide for the management of recurrence in patients affected by urinary stones<sup>6</sup>. Ettinger et al., published in 1997 one of the first clinical trial on the use of potassium-magnesium citrate in preventing recurrent calcium oxalate kidney calculi, demonstrating that potassium-magnesium citrate effectively prevents recurrent calcium oxalate stones<sup>7</sup>. Focusing on the plant extracts, *Phyllanthus niruri*, commonly known as "stone-breaker", is able to increase urinary excretion of magnesium and potassium caused a significant decrease in urinary oxalate and uric acid in patients with hyperoxaluria and hyperuricosuria, contributing to the elimination of urinary calculi<sup>4</sup>. Moreover, *Chrysanthellum americanum* seems to be effective in the reduction of stone formation, probably due to the effect of chrysantellin, a saponin, on the stone aggregation<sup>8</sup>. Starting from these evidences, we aim to evaluate the efficacy of a medical device containing *Phyllanthus niruri* and *Chrysanthellum americanum* in association with potassium and magnesium citrates in the treatment and prophylaxis of symptomatic episode in patients affected by recurrent uncomplicated urinary stones.

## MATERIALS AND METHODS

### Study schedule and population

From January 2018 to March 2019, all patients attending two referral institutions with history of recurrent uncomplicated urinary stones were enrolled in this prospective phase II study. All enrolled patients underwent a urological visit for inclusion and exclusion criteria assessment with quality of life (QoL) questionnaires, serum chemistry, urinalysis and non-contrast-enhanced CT scanner. All patients were encouraged to make lifestyle changes and received a food supplement containing *Phyllanthus niruri* and *Chrysanthellum americanum* in association with potassium and magnesium citrates, one capsule a day for 6 months. After 3 months, all patients were contacted by phone by the trialists in order to check the adherence to the treatment. After 6 months, all patients underwent urologic visit, urinalysis, instrumentation and QoL questionnaires evaluation. **Figure 1** shows the study schedule.

### Outcome measures

The main outcome measures were the reduction of symptomatic episodes and improvement in questionnaire result from baseline at the end of the follow-up period. Stone dimension reduction and stone-free rate at 6 months follow-up CT scan was also considered as secondary outcome measures.

### Inclusion and exclusion criteria

We considered for the inclusion, all patients with CT demonstration of one or multiple stones up to 15 mm. All patients with the following characteristics were excluded: serum creatinine level >1.6mg/dL, microbiological demonstration of urinary tract infection, non-controlled diabetes, chronic liver disease and all the other serious comorbidities. Moreover, all patients with the evidence of ureterohydronephrosis or renal colic were excluded. Pregnant women were excluded, too.

### Patients' clinical, laboratory and instrumental assessment

At the baseline, all patients underwent urological visit with quality of life (QoL) questionnaires, serum chemistry and blood analysis, urinalysis and non-contrast-enhanced CT scanner. The identified calculi were classified according to their number, location (superior, middle, inferior calyx) and size. Clinical data comprised systolic and diastolic blood pressure and anthropometric evaluation (weight, height, body mass index (BMI)). Serum chemistry and blood analysis comprised blood count, assessment of urea, creatinine, sodium, potassium, glucose, uric acid, total and ionized calcium, total cholesterol and fractions, triglycerides, alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transpeptidase, amylase and bilirubin levels. Urinalysis with urinary pH measurement and a urine culture was performed using spontaneous voided urine.

### Questionnaires

The impact of symptomatic episodes of renal stones on patients' QoL has been evaluated by using an Italian version of the Quality of Well-Being, a validated, multi-attribute health scale<sup>9</sup>. This scale was selected because it has been successfully applied to acute illnesses, whereas other quality of life scales, including the Short Form-36 (SF-36) Health Survey, are more suitable in chronic cases. Higher scores on the QoL scale reflect a higher quality of life<sup>10</sup>.

### Follow-up and efficacy assessment

After treatment, all patients were reassessed by urologic visit with questionnaire, serum chemistry and blood sample, urine analysis and instrumentations, in order to evaluate the changes in number, location and size of the calculi at 3 and 6 months. At 3 months all patients underwent urinary tract sonography and at 6 months non-contrast-enhanced CT scanner. At 3 months the stone evaluation has been performed by using urinary tract sonography in order to reduce the patients' exposition to X-ray. However, the stone free-rate has been calculated between the baseline and the 6 months follow-up CT scan.

### Compounds characteristics

All patients were treated in line with the manufacturer's instructions (Erbozeta S.p.A., RSM - <https://www.erbozeta.com>). Each administration contained a combination of the following ingredients: Citrates (of Potassium and Magnesium), Phyllanthus (*Phyllanthus niruri*) herb d.e. 15% Tannins, Chrysanthellum (*Chrysanthellum americanum*) plant d.e. 1/4.

### Statistical and Ethical considerations

As null hypothesis, we consider that there is no difference in terms of number of symptomatic episodes and QoL between baseline and the end of the follow-up evaluation. In order to obtain significant results to analyze, sample size calculation was based on the following assumptions: difference in terms of QoL between baseline and follow-up visit:  $+ 0.3 \pm 0.06$ ;  $\alpha$  error level, 0.05 two-sided; statistical power, 80%; anticipated effect size, Cohen's  $d = 0.5$ . The calculation yielded 72 individuals. Considering a drop-out rate of 10%, the final sample size was set to 79 patients. The statistical analysis was performed as follows: continuous variables are presented as median and InterQuartile Range (IQR) and categorical variables are presented as absolute (n) and relative (%) frequency distributions. t-tests were used to compare average performance between enrolment and the follow-up evaluation, and between the periods before and after enrolment. The statistical analysis was performed using SPSS. Due to the fact that this food supplement is already present in Italian pharmacopeia and that *Phyllanthus niruri* has been approved for the management of patients affected by urinary stones in Italy, the study did not require approval by the local ethics committee (IRB). Nevertheless, our study was conducted in line with Good Clinical Practice guidelines and the ethical principles laid down in the latest version of the Declaration of Helsinki. Before inclusion, all participants signed the written informed consent about personal data collection and storage, in accordance with national bylaws. All anamnestic, clinical and laboratory data containing sensitive information about patients were de-identified in order to ensure analysis of anonymous data only.

The de-identification process was performed by non-medical staff by means of dedicated software. A placebo run-in period was considered unnecessary.

## RESULTS

From January 2018 to March 2019, 82 patients (mean age  $49.7 \pm 11.2$ ) completed the follow-up period and were analyzed.

### Baseline

At the baseline, the average stone size was 7.8 mm and 23 patients showed asymptomatic bacteriuria (ABU). The most common isolated strain was *Enterococcus faecalis* (18/23; 78.2%). The median number of symptomatic episodes at baseline was 3 per year. The median number of calculi was 1 (range: 1-4). In 38 patients (46.3%) the calculi were located in the right kidney, 36 (43.9%) had left kidney lithiasis, while 8 patients had bilateral kidney lithiasis (9.8%). No difference, from the normal values, has been reported in terms of urine analysis parameters among the enrolled patients. The **table 1** shows all demographic and baseline clinical and instrumental characteristics of enrolled patients.

Table 1. Patient clinical, instrumental and laboratory characteristics at the baseline.	
<i>No. of enrolled patients</i>	82
<i>Median age (<math>\pm</math>SD)</i>	$49.7 \pm 11.2$
<i>Sex</i>	
Male	49 (59.7)
Female	33 (40.3)
<i>Body Mass Index (BMI)(<math>\pm</math>SD)</i>	$25.8 \pm 6.3$
<i>Charlson Comorbidities Index</i>	
0	75 (11.5)
1	7 (8.5)
2	-
<i>Start of urinary lithiasis (years) (range)</i>	$2.3 \pm 0.9$
<i>Number of symptomatic episodes per year (<math>\pm</math>SD)</i>	$3 \pm 1.2$
<i>History of any endourological treatment (in the last 6 months)</i>	
Yes	12 (14.6)
No	70 (85.4)
<i>Number of stones (range)</i>	1 (1-4)
<i>Mean stone size (<math>\pm</math>SD)</i>	$7.8 \pm 1.1$
<i>Stones side</i>	
Right kidney	38 (46.3)
Left kidney	36 (43.9)

<i>Bilateral</i>	8 (9.8)
<i>Mean hounsfield units (±SD)</i>	637.1 ± 264.8
<i>Stones location (calyx)</i>	
<i>Superior</i>	30 (36.5)
<i>Middle</i>	38 (46.4)
<i>Inferior</i>	14 (17.1)
<i>Presence of asymptomatic bacteriuria</i>	
<i>Yes</i>	23 (28.1)
<i>No</i>	59 (71.9)
<i>Isolated strains</i>	
<i>Enterococcus faecalis</i>	18 (78.1)
<i>Escherichia coli</i>	3 (13.3)
<i>Klebsiella spp.</i>	2 (8.6)

**Table 1:** The table shows all patient clinical and microbiological characteristics at the time of enrolment. Data in parentheses are percentages unless otherwise specified. Abbreviations: SD, Standard Deviation.

### 6 months follow-up

#### *Adherence to the life-style changes and treatment*

At the 3 months follow up telephone contact, 50 patients reported a high adherence to the life-style changes and to the treatment. At the end of the follow-up period, the adherence to the life-style changes and to the treatment was total in 60 patients (73.1%), while in twenty-two patients (26.8%) some minimal missing doses have been registered. A significant improvement has been reported between the 3- and 6-months evaluations in terms of adherence to the treatment and the life-style changes.

#### *Clinical and instrumental outcomes and QoL*

Twenty-seven patients out of 82 were stone-free (32.9%) at the end of the follow-up evaluation, while 50 patients showed lower stones dimension (60.9%). The average stones size at the end of the follow-up was 0.9 mm, with a significant reduction in comparison with the baseline (-6.7 mm ±3 mm) ( $p < 0.001$ ). Forty-nine patients (59.7%) did not show any symptomatic episode with an improving in QoL (+0.4 ±0.1) ( $p < 0.001$ ) in comparison to the baseline. No difference, from the normal values, has

been reported in terms of urine analysis parameters among the enrolled patients. The table 2 shows all clinical and instrumental findings at the end of the follow-up.

Table 2. Clinical, instrumental and laboratory findings at each follow-up visit (3 and 6 months after treatment).		
	3 months	6 months
<i>Adherence to life-style changes recommendations</i>		
Patients with a high grade of adherence	50 (60.9)	60 (73.1)
<i>Clinical improvement</i>		
Recurrence-free patients	38 (46.3)	49 (59.7)
QoL improvement	+0.3 ±0.2	+0.4 ±0.1
Difference from baseline	p<0.001	p<0.001
<i>Stone-free status</i>		
	19 (23.1)	23 (32.9)
<i>Stone size reduction (mm)</i>		
Difference from baseline	-4.2 ±2	-6.7 ±3
	p<0.001	p<0.001
<i>Presence of asymptomatic bacteriuria</i>		
	9 (10.9)	3 (3.6)
Difference from baseline	p<0.001	p<0.001

**Table 2:** The table shows all clinical, instrumental and laboratory findings at 3 and 6 months of follow-up. Abbreviations: QoL: Quality of Well-Being.

#### *Asymptomatic bacteriuria*

At the end of follow-up evaluation, 3 patients reported ABU. A significant reduction of patients with ABU between the baseline and the end of the follow-up evaluation (23 vs 3; p<0.001) has been reported. A significant correlation between ABU reduction and stones number and dimension reduction has been reported (r=0.83; p<0.001).

#### *Adverse effects*

No clinically significant adverse effects have been reported.

## **DISCUSSION**

We demonstrated that a food supplement containing *Phyllanthus niruri* and *Chrysanthellum americanum* in association with potassium and magnesium citrates is able to improve quality of life in patients with urinary stones, reducing symptomatic episodes, stones number and dimension and the

prevalence of asymptomatic bacteriuria. Two important points should be discussed: the role of phytotherapy in the management of urinary stones and its mechanism of action and the relationship between urinary stones and asymptomatic bacteriuria.

#### Role of phytotherapy in the management of urinary stones and mechanism of action

Phytotherapy is one of the first choices regarding pharmaceutical treatment of patients affected by urinary stones<sup>2</sup> due to the demonstrated efficacy<sup>4,11</sup> and due to the patient's preference for phytotherapeutic compounds. Micali and Pucci, in two clinical trials, demonstrated that *Phyllanthus niruri* is able to reduce the stone size and improve the stone free status rate<sup>4,11</sup>. In line with these trials, we found a significant reduction in terms of stones size in comparison with the baseline (-6.7 mm  $\pm$  3 mm) ( $p < 0.001$ ) and a high percentage of stone free patients after treatment. These interesting findings are probably due to *Phyllanthus niruri* and *Chrysanthellum americanum* combination in association with potassium and magnesium citrates. The efficacy of *Phyllanthus niruri* is probably augmented by the presence of *Chrysanthellum americanum*. The role of *Chrysanthellum americanum* in the management of urinary stones is due to its interference, through the chrysantellin, a saponin, with some stages of crystallization in urine, such as a reduction in the nucleation, growth and aggregation of calcium oxalate crystals<sup>8</sup>. Moreover, the synergistic effect of *Phyllanthus niruri* and *Chrysanthellum americanum* is probably due to its diuretic effects<sup>12-13</sup>. Furthermore, our food supplement contains potassium and magnesium citrates, although previous studies did not favor potassium citrate therapy. However, potassium can moderate the concentration of sodium in urine and promote the elevation of citrate, which acts to correct urinary pH and acidity, possibly contributing to an increase in calcium solubility and, then, interfere with some stages of crystallization in urine<sup>14-15</sup>. Our food supplement is, then, able to act into two different pathways: diuresis increasing and inhibition of nucleation, growth and aggregation of calcium oxalate crystals. Moving to the role of life-style changes, we found a significant improvement between the 3- and 6-months evaluations in terms of adherence to the treatment and life-style changes. The clinical reported efficacy in terms

of reduction of symptomatic episodes, due to the treatment, drives the adherence to the life-style changes. In this sense, this food supplement should be considered, also, as an interesting tool for driving the adherence to the life-style changes and for obtaining a long-term efficacy on the stone recurrence. The high adherence to the treatment is due to the absence of reported adverse effects, too.

#### *Relationship between urinary stones and asymptomatic bacteriuria*

This was the first study that analyzed the efficacy of a food supplement in reducing asymptomatic bacteriuria in patients affected by urinary stones. Asymptomatic bacteriuria is a common clinical condition among recurrent stones patients, which does not generally require any treatment. However, the role of asymptomatic bacteriuria in patients with recurrent urinary stones is not completely understood. Here, we demonstrated that this food supplement is able to statistically significantly reduce the prevalence of asymptomatic bacteriuria among recurrent stone patients. The efficacy on asymptomatic bacteriuria is probably due to the increasing of total daily diuresis, thanks to *Phyllanthus niruri* and to the inhibition of nucleation, growth and aggregation of bacterial biofilm on the surface of calcium oxalate crystals, thanks to *Chrysanthellum americanum* action. Finally, the role of bacteria biofilm on the urinary stone aggregation is another important field to deeply explore. Future studies are needed to confirm these hypotheses.

## **CONCLUSIONS**

In conclusion, this food supplement containing *Phyllanthus niruri* and *Chrysanthellum americanum* in association with potassium and magnesium citrates is able to reduce symptomatic episodes, improving quality of life in patients with urinary stones and reduce the prevalence of asymptomatic bacteriuria.

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