

# A pilot randomized study comparing *Blumea balsamifera* (sambong) and terpenes on ureterolithiasis

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## Abstract

**Introduction** Alternative agents have been proposed for the management of kidney or ureteral stones. This study aimed to investigate the safety and efficacy of *Blumea balsamifera* (sambong) compared with a terpene combination drug as treatment for ureterolithiasis.

**Methods** Patients with clinically stable kidney function and ureteral stones of  $\leq 5$  mm were randomized to receive a special terpene combination (Rowatinex®) or *Blumea balsamifera*. All patients had a physical examination, and diagnosis of kidney stones was made by ultrasound at baseline and after 6 and 12 weeks of treatment. Primary outcomes were change in stone size and stone-free status, defined as obviously successful expulsion of calculi/fragments, documented by ultrasound.

**Results** After 6 weeks, five patients in the sambong group and six in the terpene group were stone free ( $p = 0.90$ ). After 12 weeks, seven in the sambong and eight in the terpene group were stone free ( $p = 0.31$ ). In terms of stone size, there was a significant decrease in the mean diameter in the sambong group ( $1.81 \pm 2.01$  mm,  $p = 0.008$  and  $1.12 \pm 1.43$  mm  $p < 0.005$ ) and in the terpene group ( $1.24 \pm 1.43$  mm  $p < 0.005$  and  $0.74 \pm 0.70$  mm,  $p < 0.005$ ) at 6 and 12 weeks, respectively. However, there was no significant difference between the two groups. Urine pH also increased in both groups compared to baseline but the difference was not statistically significant when comparing the two arms.

**Conclusion** *Blumea balsamifera* is comparable with a terpene combination in the dissolution of urolithiasis and is well-tolerated and safe.

**Key words:** Urinary calculi, terpenes, herbal medicine

The incidence of urinary tract stones in the Philippines is not available, however, among

Asian countries, it ranges from 5 to 25%.<sup>1</sup> In a study done at a tertiary government hospital, this condition was found to be more common in males during the late adult period, usually presenting as bladder stones (cystolithiasis).<sup>2</sup> The possibility of recurrence increased with time, as approximately 10% would have had a new episode within a year, 50% in 5 to 10 years and up to 75% in 20 years.

There are different types of urinary tract stones. The most common type, even in the local setting, is calcium oxalate stones of the mixed type, which

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comprised almost 60% of the cases in the aforementioned local study.<sup>2</sup> Hypocitraturia is also another common problem, with lower urinary citrate found in Filipino stone formers, compared to non-stone formers.<sup>3</sup> Metabolic, radiologic and urinary investigations are therefore paramount in determining the type and severity of these stones.

Management may be either surgical or medical. Surgical treatment depends on the size, location, symptoms and presence of obstruction. If the ureteral stone is larger than 10 mm, and pain persists despite pain relievers, endoscopic removal may be done. However, if this is not possible, a ureteral stent or nephrostomy tube may be inserted until URS can be carried out. Extracorporeal shockwave lithotripsy, laser removal and percutaneous lithotomy are other options.<sup>4</sup>

Medical management meanwhile includes increased fluid intake and dietary modification.<sup>4</sup> Fluid intake should be primarily water and goal urine volume should be at least 2 liters daily. With regards to food intake, reduction in foods rich in oxalates, fats, animal protein have also been found to be beneficial. Dietary plans should be individualized, depending on the metabolic problems noted on work-up.

Pharmacologic treatment can also be given depending on the stone type. There are medications that also promote increased urine volume, stone expulsion and alkalization of the urine. Terpenes is one of these medications that have been investigated in various studies. Its exact mechanism of action is not known but some of these terpenes include pinene and fenchone, which are said to have anti-bacterial properties. Cineole and anethole meanwhile exert anti-inflammatory and analgesic activities. Camphene and borneol were shown to have anti-spasmodic effects on smooth muscles in animal studies.<sup>5</sup>

In a randomized placebo-controlled trial by Engelstein in 1992, terpenes had a significantly higher expulsion rate of ureterolithiasis (81% vs. 59%) with a good safety profile.<sup>6</sup> However, in another study in patients with distal ureteral stones less than 10 mm in diameter, terpenes showed lower expulsion rates than tamsulosin.<sup>7</sup> It also had varying stone clearance rates among post-extracorporeal shock wave lithotripsy patients in placebo-controlled trials.<sup>8,9</sup>

In the Philippines, *Blumea balsamifera* (known locally as sambong) has also been used as part of medical management of urinary tract stones. Sambong is a coarse, erect, strongly aromatic shrub commonly found in open grasslands. It has been used as herbal medicine for fever, headache, boils, abdominal pain, cough and gaseous distention. It was discovered accidentally as a diuretic when initial studies for other medicinal purposes noted that subjects complained of increased frequency of urination.<sup>10</sup> A pilot study by de Leon and Maramba in 1984 showed that sambong had comparable diuretic properties with thiazide, had a rapid onset (within 30 minutes), and did not have any significant effect on serum electrolytes.<sup>11</sup>

In the 1990s, there were further studies on sambong as part of urinary tract stone treatment. In a randomized, double-blind placebo-controlled trial by Sigua and Molina, there was a higher proportion of patients with complete passage after 4 weeks of sambong compared to placebo (31% vs. 8%) and significant reduction of stone size based on radiographic imaging.<sup>12</sup> Another trial showed a higher rate of complete passage (55%) compared to placebo.<sup>13</sup> Almost 90% of the patients had radiographic improvement of the stone and there were similar rates of acceptability in terms of taste, smell and ease of swallowing.

The only head-to-head study comparing sambong with another medication was an open label study with potassium citrate.<sup>14</sup> No other published studies have been done on sambong for urinary tract stones. This pilot study investigated the comparability of sambong with terpenes in terms of dissolution effect and safety among patients with non-obstructing urolithiasis.

## Methods

The study was done from January to June 2017 at the San Antonio District Hospital, a 50-bed primary level facility ran by the Provincial Government of Nueva Ecija. The study was approved by the Provincial Health Office and the hospital's Ethics Committee. The subjects comprised of clinic patients newly diagnosed with ureterolithiasis. Initial screening through history taking and physical examination was done. Patients included were adults 18 years old and above with ureterolithiasis up to 5

mm based on ultrasound. Subjects were excluded if they had 1) clinical signs of urinary tract obstruction, 2) active infection, 3) renal insufficiency defined as estimated glomerular filtration rate (eGFR) of less than 60 ml/min/1.73m<sup>2</sup> by MDRD equation, and 4) patients on diuretics regardless of the indication.

Informed consent was obtained from each patient. Afterwards, baseline laboratory work-up with urinalysis and blood chemistries were obtained. A baseline ultrasound was performed. The operator and reader were blinded to the clinical data of the subjects, other than the diagnosis of urinary tract stones. A research assistant randomized the patients to either Group A where patients received sambong 500mg/tablet, taken two tablets, three times a day or Group B, who were given the terpene combination (Rowatinex®) two capsules, three times a day for three months. Both medications were packaged in blister packs and placed in opaque envelopes marked A or B. In addition, all patients were given tamsulosin 400ug/tablet, one tablet daily. Instructions on proper diet and increased fluid intake were given.

Patients were instructed to follow-up weekly on the first month to monitor for adverse events or other medical concerns. On the 6th week, patients were requested to follow-up for repeat diagnostics and ultrasound. If there were no problems, follow-up was done every two weeks until the end of the third month (12 weeks). Another set of blood chemistries, urine testing and ultrasound were performed. A subject who failed to come back at least twice was classified as drop-out and the reason for dropping out was recorded.

The primary outcome of the study was complete dissolution of stone, as documented on ultrasound. Other outcomes include stone size, urine pH, serum chemistries and adverse outcomes. Other than the adverse events, the variables were collected at 6 and 12 weeks of treatment. Non-numerical variables were expressed as frequencies with percentages and analyzed by chi-square test. Numerical variables were expressed as mean + standard deviation (SD), and analysis of variance (ANOVA) was done.

## Results

Forty subjects were recruited in the study from January to June 2017, 20 in each arm. Before the 4th week, three subjects from each group were dropped

for lack of compliance, leaving 17 in each treatment arm. Table 1 shows the baseline characteristics of both treatment groups. There were no statistical differences among the variables presented. All lithiasis were in the mid- to distal third of the ureter.

**Table 1.** Baseline characteristics of 34 subjects.

	Sambong Group (n=17) n (%)	Terpene Group (n=17) n (%)
Gender		
Male	8 (47.1)	7 (41.2)
Female	9 (52.9)	10 (58.8)
Age (years ± SD)	47.6 ± 14	47.5 ± 12
Co-morbidities		
Diabetes	2 (11.8)	4 (23.5)
Hypertension	3 (17.6)	4 (23.5)
Dyslipidemia	6 (35.3)	5 (29.4)
Laterality		
Left	6 (35.3)	8 (47.1)
Right	11 (64.7)	9 (52.9)
Other tract stones		
Nephrolithiasis	2 (11.8)	4 (23.5)
Cystolithiasis	1 (5.9)	0

Table 2 shows the primary stone outcomes of both treatment groups. After 6 weeks, five patients in the sambong group and six subjects in the terpene group were stone-free (p = 0.90). After 12 weeks, 41.2% in the sambong group and 47.1% in the terpene group were stone-free (p = 0.31). In terms of stone size, there was a significant decrease in the mean stone size after 6 weeks (1.81 ± 2.01 mm, p = 0.008) and 12 weeks (1.12 ± 1.43 mm p < 0.005) in the sambong group, and in the terpene group (1.24 ± 1.43 mm, p < 0.005 at 6 weeks and 0.74 ± 0.70 mm, p < 0.005 at 12 weeks). However, there was no significant difference between the two groups. Urine pH also significantly increased in both groups compared to baseline but the difference between the two arms was not significant.

Table 3 shows the serum chemistries in both groups. There were no significant differences in the serum sodium, potassium, creatinine and ionized calcium between the treatment arms. However, serum

uric acid in the sambong group showed a significant decrease after 12 weeks of treatment compared to the terpene group. There was also a significant decrease

in the serum uric acid in the sambong group compared at their baseline values and at 6 weeks of treatment.

**Table 2.** Stone outcomes on patients treated with sambong and terpenes.

	Stone Size (mm)		Stone Free		Stone Unchanged		Stone Decrease Size		Urine pH	
	Sambong	Terpene	Sambong	Terpene	Sambong	Terpene	Sambong	Terpene	Sambong	Terpene
Baseline	2.98±1.02	3.01±0.88							5.82±0.34	5.85±0.55
6 weeks {p vs baseline}	1.81±2.01 {0.008}	1.24±1.43 {<0.005}	5	6	3	1	9	11	6.64±0.30 {<0.005}	6.41±0.35 {0.02}
P-value in 2 groups	0.22				0.9				0.23	
12 weeks {p vs baseline}	1.12±1.43 {<0.005}	0.74±0.70 {<0.005}	7	8	3	3	8	6	6.64±0.14 {<0.005}	6.58±0.19 {<0.005}
P-value in 2 groups	0.30				0.31				0.68	

**Table 3.** Serum chemistries of sambong and terpene groups

	Sambong Group (n=17)	Terpene Group (n=17)
Serum Na (mmol/L)		
Baseline	142.2 ± 21	142.2 ± 77
6 weeks	141.6 ± 12	142.3 ± 11
12 weeks	142.1 ± 13	141.5 ± 14
Serum K (mmol/L)		
Baseline	4.2 ± 0.15	4.3 ± 0.18
6 weeks	4.2 ± 0.10	4.3 ± 0.07
12 weeks	4.2 ± 0.09	4.2 ± 0.04
Ionized calcium (mg/dL)		
Baseline	4.9 ± 0.03	5.0 ± 0.04
6 weeks	4.9 ± 0.04	5.1 ± 0.02
12 weeks	5.0 ± 0.03	5.0 ± 0.02
Serum creatinine (mg/dL)		
Baseline	1.1 ± 0.05	1.0 ± 0.05
6 weeks	1.1 ± 0.04	1.0 ± 0.02
12 weeks	1.1 ± 0.06	1.1 ± 0.08
Serum uric acid (mg/dL)		
Baseline	6.3 ± 0.77	6.3 ± 0.47
6 weeks	6.2 ± 0.45	6.2 ± 0.32
12 weeks	6.0 ± 0.16 <sup>a,b,c</sup>	6.1 ± 0.17

Note: <sup>a</sup> p = 0.02 vs uric acid terpene at 12 weeks  
<sup>b</sup> p = 0.01 vs uric acid sambong at 6 weeks  
<sup>c</sup> p = 0.003 vs uric acid sambong at baseline

There were no differences in adverse events and only mild symptoms were reported. There were 3 and 5 episodes of nausea in the sambong and terpene groups, respectively. Four subjects in sambong group and three in the terpene group developed urinary tract infections. All UTIs showed mild pyuria and were treated accordingly with antibiotics. No hospitalizations nor deaths were noted.

### Discussion

In non-obstructing urinary tract stones, medical management is a practical and acceptable treatment. The terpene drug used in this study is a combination of seven essential oils with the previously mentioned effects. It may promote diuresis through increased renal blood flow. It was introduced in the 1950s and still used worldwide as part of medical management. In the present study, the stone-free rates of patients given terpenes are comparable with previous studies by Engelstein in 1992 and Aldemir.<sup>6,7</sup> Most of the studies published on efficacy are case reports and majority had a duration of only 4 weeks.

Sambong, meanwhile has been used locally and in other tropical countries but available data on efficacy are limited. The only published randomized trial compared sambong with placebo and potassium citrate.<sup>14</sup> Results showed sambong had a 37% stone-free rate at the end of 2 months, compared to 25% in the placebo and 50% in the potassium citrate groups; the present study had a rate of 41%. Compared with placebo, sambong also showed significant decrease in mean stone size, which was also the trend in the present study.

The study shows that patients treated with sambong had statistically similar stone dissolution rates. However, in terms of average stone size, those treated with sambong had a smaller mean diameter than those given terpenes. Multiple mechanisms have been elucidated. In a kinetic study, sambong increased crystallization and nucleation rates, leading to tendency to form smaller-sized crystals which are easier to eliminate.<sup>15</sup> As a diuretic, it significantly increased urine volume, and urine sodium and chloride excretion with minimal kaliuresis.<sup>11</sup> As mentioned earlier, its diuretic effect was comparable to thiazides, which is given in cases with hypercalciuria. It is also said to have muscle relaxant properties.<sup>16</sup>

Another result in this study was a significantly lower serum uric acid among patients treated with sambong. Its uric acid lowering ability may be due to xanthine oxidase inhibition. In a study comparing different medicinal plants available locally, *Blumea balsamifera* was shown to have the highest xanthine oxidase inhibition at 79.67%, with *M. pudica* having the next highest inhibition at 62.36%.<sup>17</sup> It should be noted that allopurinol was given to five patients in the sambong group and four in the terpene group. However, there was no significant difference with the proportion of those given uric acid lowering medications, hence the interventional drug may have contributed to the lowering of mean serum uric acid. The study also showed a good safety profile in those treated with sambong and terpenes. This increases compliance of the medication, possibly making it more efficacious.

This is the first study on ureterolithiasis that compared sambong with terpenes. The strength of this study was that the treatment duration was longer (12 weeks) as compared to other randomized trials. It focused on a specific type of urinary tract stone (ureterolithiasis) to avoid heterogeneity. Also, most studies of this nature focused only on stone-free rates. This study included some serum chemistries, which are recommended by guidelines to be a part of work-up to determine possible stone type and the need for adjunct medications.<sup>18</sup>

The study has several limitations. While treatment covered 12 weeks, it was not long enough to determine long-term effects and recurrence rates. The only urinary test done was a routine urinalysis. Ideally, other urine chemistries should also be performed to determine other possible causes of stone formation. Despite these limitations, the study showed that treatment with *Blumea balsamifera* in patients with small-sized ureterolithiasis is comparable to terpenes in terms of efficacy and is well-tolerated and safe.

**Conflict of interests** None to declare

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