Evaluation of efficacy and safety of a herbal formulation Cystone in the management of urolithiasis: Meta-analysis of 50 clinical studies

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Abstract
Systematic reviews form a potential method for overcoming the barriers faced by clinicians when trying to access and interpret evidence to help in their practice. Clinical trials give the evidence regarding efficacy/safety or otherwise about a treatment model or medication. These studies need to be looked at with a perspective of creating evidence-based healthcare. Meta-analysis is a process of combining study results that can be used to draw conclusions about therapeutic effectiveness or otherwise. The aim of the study is to carry out the meta-analysis of 50 clinical trials for identifying the efficacy and safety of Cystone in urolithiasis. In all, 50 clinical studies done at various centers between 1954 and 2004 have been taken into account, which involved 3037 patients (Cystone: 1837 and others: 1200 of either sex). From each study, the demographic data of patients on entry was tabulated. The duration of treatment has varied from 2 weeks to 2 years and in most of the studies, except in pediatric patients, Cystone was used in the dose of 2 tablets thrice daily. Parameters such as size of renal calculi, clearance of calculi with reference to location of calculi, symptomatic relief and urinary excretion of stone forming constituents were...
evaluated. Statistical analysis was done using Fisher’s exact test, paired ‘t’ test or repeated measures of ANOVA followed by Dunnett’s multiple comparison test. The minimum level of significance was fixed at 95% confidence limit and a 2-sided p value of <0.05 was considered significant. Statistical analysis was performed using GraphPad Prism software (Version 4.01). Cystone is efficacious in management of urolithiasis especially when the site of urinary stone is ureter or kidney. This study indicated a significant symptomatic relief in Cystone group. Cystone treatment revealed a significant reduction in 24-hour urinary excretion of oxalate (p<0.01), uric acid (p<0.01), calcium (p<0.01), magnesium, and phosphorus with a significant increase in urine volume (p<0.01). This analysis also indicates the safety profile of Cystone. The adverse effects have been very mild like dyspepsia, flatulence and gastric irritation, which did not necessitate the withdrawal of the drug. There have been no reports of any serious adverse effects. Similarly, there is no report of mortality due to Cystone. The outcome of 50 clinical studies indicated that Cystone is useful in the management of urolithiasis as revealed by the clearance of calculi, symptomatic relief, increased urine volume, and reduction in the stone forming constituents in urine with negligible adverse effects.

**Introduction**

Systematic reviews form a potential method for overcoming the barriers faced by clinicians when trying to access and interpret evidence to help in their practice. Evidence-based healthcare is the integration of best research evidence with clinical expertise and patient values. Using evidence from a reliable research to inform healthcare decisions has the potential to ensure best practice and reduce variation in healthcare deliveries. However, incorporating research into practice is time consuming and so methods that can facilitate easy access to evidence for a busy clinician is required.

Clinical trials give the evidence regarding efficacy/safety or otherwise about a treatment model or medication. These studies need to be looked at with a perspective of creating evidence-based healthcare. Meta-analysis is a process of combining study results that can be used to draw conclusions about therapeutic effectiveness or otherwise. Meta-analysis can be performed when the studies are similar with respect to population outcome and intervention. Meta-analysis (quantitative synthesis or overview analysis) is a term used to describe quantitative methods for combining information across different studies.

A meta-analysis is a two-stage process; the first stage is the extraction of data from each study and the calculation of the result for each study. The second stage involves deciding whether it is appropriate to calculate a pooled average result across studies. This process gives greater weightage to the results from the studies that give more information because these are likely to be closer to the truth we are trying to estimate.
Urolithiasis or renal calculi are crystal aggregations of dissolved materials in the urine and hence the process is called urolithiasis. The sequence of formation of urinary stone involves urinary saturation, urinary supersaturation, nucleation, crystal growth, crystal aggregation, and urinary stone formation. Urinary stones are formed because of metabolic disturbances like hypercalciuria, hyperoxaluria, cystinuria, etc. Sometimes, urinary stones are formed because of chronic urinary tract infections (UTI). Urinary stones can be calcium stones, cystine stones, uric acid stones, or struvite stones. They typically form inside the kidney (nephrolithiasis), ureter (uro lithiasis), or urinary bladder. These calculi can vary in size and shape and when they grow up to 2.3 mm, they can cause obstruction of the ureter. This may lead to obstruction with dilation or stretching of the upper ureter and renal pelvis as well as spasm leading to severe episodic abdominal pain, which may be associated with nausea and vomiting. At present, no medical therapy is available for dissolution or displacement of renal stones.

A number of herbs and their combinations have been claimed to have beneficial effects in urolithiasis. Cystone is a herbomineral formulation specifically developed for the management of urolithiasis or renal calculi.

Composition of each Cystone tablet*

<table>
<thead>
<tr>
<th>Composition</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Didymocarpus pedicellata</em></td>
<td>65 mg</td>
</tr>
<tr>
<td><em>Saxifraga ligulata</em></td>
<td>49 mg</td>
</tr>
<tr>
<td><em>Rubia cordifolia</em></td>
<td>16 mg</td>
</tr>
<tr>
<td><em>Cyperus scariosus</em></td>
<td>16 mg</td>
</tr>
<tr>
<td><em>Achyranthes aspera</em></td>
<td>16 mg</td>
</tr>
<tr>
<td><em>Onosma bracteatum</em></td>
<td>16 mg</td>
</tr>
<tr>
<td><em>Vernonia cinerea</em></td>
<td>16 mg</td>
</tr>
<tr>
<td>Shilajeet (Purified)</td>
<td>13 mg</td>
</tr>
<tr>
<td>Hajrul yahood bhasma</td>
<td>16 mg</td>
</tr>
</tbody>
</table>

*In the present tablet of Cystone, the individual ingredients are doubled and the dosage is reduced to half.

This product was introduced in Indian Medical Practice in the year 1943; since then, more than 3200 million tablets have been sold. This formulation is being used extensively in the management of urolithiasis. Till date, 80 clinical trials have been carried out to evaluate the safety and efficacy of Cystone in the management of
urolithiasis. The present study was carried out to review the meta-analysis of 50 of these clinical trials, so as to arrive at the status of Cystone in the management of urolithiasis.

**Aim of the study**
The aim of the study is to carry out the meta-analysis of 50 clinical trials for identifying the efficacy and safety of Cystone in urolithiasis.

**Material and Methods**

**Study design**
This is a cumulative meta-analysis of 50 published clinical trials of Cystone in Urolithiasis.

**Study period**
This study evaluated the clinical trials of Cystone conducted between 1954 and 2004.

**Inclusion criteria**
All published studies, which evaluated the role of Cystone in urolithiasis, were included in the meta-analysis irrespective of the study design, as most of these research papers were carried out in India when randomized clinical trials were not being commonly carried out. The meta-analysis includes clinical trials, which were either controlled studies or open clinical studies. There were no restrictions regarding sex, age, or duration of disease. The outcome variables included measurement data on changes in clinical symptoms and signs, laboratory results, and incidence of adverse events during/after treatment.

**Exclusion criteria**
Experimental Phase I and Phase II studies were excluded from the study population.

**Study procedure**
In all, 50 clinical studies done at various centers between 1954 and 2004 were taken into account (Appendix Table 1). From each study, the demographic data of patients on entry was tabulated. The duration of treatment varied from 2 weeks to 2 years (Table 2) and in most of the studies, except in pediatric patients, Cystone was used in the dose of 2 tablets thrice daily. Changes in the clinical and biochemical parameters were taken into account in addition to the calculi size, location of the calculi, urine volume and urinary excretion of oxalate, uric acid, and calcium. Studies that considered parameters like burning micturition, bacteriuria, and the presence or absence of pus cells in the urine of urolithiasis patients, were also taken into account.

**Adverse events**
The incidence and type of adverse events reported by various studies were also tabulated separately. All adverse events, either reported or observed by patients, were recorded with information about severity, duration, and action taken regarding the
study drug. Relation of adverse events to study medication was predefined as “Unrelated” (a reaction that does not follow a reasonable temporal sequence from the administration of the drug), “Possible” (follows a known response pattern to the suspected drug, but could have been produced by the patient’s clinical state or other modes of therapy administered to the patient), and “Probable” (follows a known response pattern to the suspected drug that could not be reasonably explained by the known characteristics of the patient’s clinical state).

**Primary and secondary endpoints**
The predefined primary endpoints in majority of these studies have been clearance of renal calculi and relief from clinical symptoms.

**Statistical analysis**
Statistical analysis was done according to intention-to-treat principles. Changes in various parameters from baseline values and values at the end of the study were pooled and analyzed cumulatively using Fisher’s Exact Test, Paired’t’ test or Repeated Measures of ANOVA, followed by Dunnett’s Multiple Comparison test. Values are expressed as Mean ± SD or as incidences of patients with or without symptoms. The minimum level of significance was fixed at 95% confidence limit and a 2-sided p value of <0.05 was considered significant. Statistical analysis was performed using GraphPad Prism software (Version 4.01).

**Results**
In all, 50 clinical trials have been taken into account, which involved 3037 patients (Cystone: 1837, Others: 1200) of either sex. The age range of patients included in all studies is 1-72 years and the duration of treatment is 2 weeks to 2 years (Table 1).

<table>
<thead>
<tr>
<th>Demographic data</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of trials</td>
<td>: 50</td>
</tr>
<tr>
<td>Number of patients</td>
<td>: 1837 (either sex)</td>
</tr>
<tr>
<td>Age of patients</td>
<td>: 1-72 years</td>
</tr>
<tr>
<td>Dose</td>
<td>: 2 tablets, t.i.d.*</td>
</tr>
<tr>
<td>Duration of treatment</td>
<td>: 2 weeks to 2 years</td>
</tr>
</tbody>
</table>

*In case of pediatric patients, ½ to 1 tablet, t.i.d.

**Table 1.** Demographic data with dose and duration of Cystone treatment

In 636 patients, data was available regarding the calculi size and analysis of this data indicates that there was a significant decrease in presence of renal calculi (Table 2) and the calculi size decreased from 6.21 ± 4.24 mm to 0.57 ± 0.79 mm (p<0.0067).
In one of the studies, antispasmodic medications, forced diuresis, and i.v. fluids were used in 50 patients, which also showed significant decrease in presence of renal calculi (Table 2).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cystone</th>
<th>Other treatment*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>Presence of renal calculi</td>
<td>636</td>
<td>78 (87.73%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(p&lt;0.0001)</td>
</tr>
<tr>
<td>Calculi size (mm)</td>
<td>6.21 ± 4.24</td>
<td>0.57 ± 0.79</td>
</tr>
<tr>
<td>(n=339)</td>
<td></td>
<td>(p&lt;0.0067)</td>
</tr>
</tbody>
</table>

*Antispasmodics (tablets in mild cases and parenteral injections in cases of severe colic), forced diuresis, and i.v. fluids.

Statistical analysis: Fisher’s Exact test for presence of renal calculi, and Paired t-test for calculi size.

**Table 2.** Effect of Cystone on clearance of renal calculi and calculi size

Coming to the effect of Cystone on clearance of calculi based on its location (Table 3), it appears that Cystone, though effective in renal, ureteric and vesical calculi, shows better results in ureteric calculi as compared to other sites. The clinical response in ureteric calculi was 89.96% whereas in renal calculi it was 73%. The results also indicate that in renal calculi, 27% of the patients required interventional surgery as compared to only 10% of patients in case of ureteric calculi (Table 3).

The meta-analysis also indicates that Cystone improves urinary volume to a significant level in 8 weeks (Figure 1). It significantly decreases oxaluria, uric acid, and calcium in the urine (Figures 2, 3).
<table>
<thead>
<tr>
<th>Location</th>
<th>No. of trials</th>
<th>No. of patients</th>
<th>Age (years)</th>
<th>Dose</th>
<th>Duration of treatment</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal</td>
<td>21</td>
<td>71</td>
<td>1-72</td>
<td>2 t.i.d. 1 t.i.d. (P)</td>
<td>2W-6M</td>
<td>52</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(73.24%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(26.76%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(p&lt;0.0001)</td>
</tr>
<tr>
<td>Ureteric</td>
<td>36</td>
<td>528</td>
<td>1-72</td>
<td>2 t.i.d. 1 t.i.d. (P)</td>
<td>2W-6Y</td>
<td>475</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(89.96%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(10.04%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(p&lt;0.0001)</td>
</tr>
<tr>
<td>Bladder/vesical</td>
<td>15</td>
<td>37</td>
<td>1-60</td>
<td>2 t.i.d.</td>
<td>2W-6M</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(83.78%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(16.22%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(p&lt;0.0001)</td>
</tr>
</tbody>
</table>

*Note: P: Pediatric patients; W: Weeks; M: Months; Y: Years
Percent response is shown in parentheses.
Statistical analysis: Fisher’s exact test.

**Table 3.** Effect of Cystone on clearance of calculi based on its location.

**Fig. 1.** Effect of Cystone on urine volume in stone formers (n=167). Data represents Mean ± SD at each week of treatment. *p<0.01 as compared to initial value. The levels observed in normal subjects (n=19) for urine volume was 2551.51 ml.
Fig. 2. Effect of Cystone on urinary excretion of oxalate in stone formers (n=222). Data represents Mean ± SD at each week of treatment. *$p<0.01$ as compared to initial value. The levels observed in normal subjects (n=19) for oxaluria was 19.93mg/24 h.

Fig. 3. Effect of Cystone on urinary excretion of uric acid in stone formers (n=119). Data represents Mean ± SD at each week of treatment. *$p<0.01$ as compared to initial value. The levels observed in normal subjects (n=19) for urine acid was 180.17 mg/24 h.
The analysis also indicates that Cystone brings about significant symptomatic relief, as compared to other treatment group, in burning micturition, and also reduces bacteuria and pus cells in patients with UTI (Table 4).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cystone Treatment</th>
<th>Other treatment</th>
<th>Protection %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Present</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Burning micturition</td>
<td>Before</td>
<td>433</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>After</td>
<td>76</td>
<td>357</td>
</tr>
<tr>
<td>Bacteuria</td>
<td>Before</td>
<td>276</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>After</td>
<td>71</td>
<td>205</td>
</tr>
<tr>
<td>Pus cells</td>
<td>Before</td>
<td>200</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>After</td>
<td>43</td>
<td>157</td>
</tr>
</tbody>
</table>

Dose: Cystone 2 tablets, t.i.d. for 1-6 months.

Other treatment: *Burning micturition*: Patients were given urinary antiseptics such as nitrofurantoin, ampicillin, cotrimoxazole, sulphonamides, or chloramphenicol alone.

*Bacteuria*: Ampicillin 250 mg, 6 hourly for 7 days, Alkaline mixture and Cotrimoxazole 2 bid for 5 days.

*Pus cells*: Conventional therapy for UTI or antibiotics prescribed based on culture sensitivity reports.

Statistical analysis: Fisher’s Exact test.

Table 4. Effect of Cystone and other treatments on burning micturition, bacteuria, and pus cells

Adverse effects
1837 patients in all had received Cystone in a dose of 2 tablets thrice a day for a period ranging from 2 weeks to 2 years. The adverse effects reported in these studies have been dyspepsia, flatulence, and gastric irritation (Table 5).

<table>
<thead>
<tr>
<th>Adverse effects</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspepsia</td>
<td>3</td>
</tr>
<tr>
<td>Flatulence</td>
<td>4</td>
</tr>
<tr>
<td>Gastric irritation</td>
<td>3</td>
</tr>
</tbody>
</table>

Table 5. Adverse drug reactions
However, none of the patients had to be withdrawn because of adverse effects. In addition, there were no reports of any serious adverse effects or of mortality due to Cystone.

**Discussion**

Humankind is known to be afflicted by urinary stone disease. Hippocrates, in the 4th century BCE, noted renal stones together with a renal abscess and wrote in the Hippocratic Oath, “I will not cut for stone”, although he was not an urologist.\(^5\)

Urinary stone disease has always been a common disease. Currently, urinary stone formation affects 10% to 12% of the population in industrialized countries and the peak incidence seems to be at ages between 20 and 40 years.\(^5\) Until the 1980s, urinary stone disease was a major health problem with a significant percent of patients undergoing severe surgical procedures for disease, in contrast to Hippocrates. Because of the morbidity and mortality of these surgical procedures, some oral drugs are used to treat this disease but adverse effects compromise their long-term consumption. On the other hand, some herbal remedies have been used to treat urinary stone disease, although scientific principles have been lacking. Today, with the understanding of many pathophysiological features underlying urinary stone disease and the mechanism of herbal remedies that can have a role in the formation and treatment of urinary stones; Phytotherapy might be an alternative treatment with an effective, safe, and culturally acceptable nature. Although some oral medications have positive effects, they are not effective in all patients. Oral citrate is one of the most widely used medical therapies for preventing urinary stone disease.\(^5\) However, this drug is not tolerated by all patients and some patients are still active stone formers during this therapy.\(^5\)

Due to the adverse effects of these drugs, alternative treatment modalities composed of herbal remedies have been the mainstay of medical therapy for thousands of years, especially in Eastern civilizations.\(^5\) Use of medicinal plants as a source of relief and cure from various illness is as old as humankind itself. Even today, medicinal plants provide a cheap source of drugs for majority of world’s population. Plants have provided and will continue to provide not only directly usable drugs, but also a great variety of chemical compounds that can be used as starting points for the synthesis of new drugs with improved pharmacological properties.\(^5\) World Health Organization has also emphasized development and utilization of herbal drugs and traditional medicines for the benefit of the world population, in terms of cost effectiveness and side effects of the drugs. The organization has also estimated that about 80% of the population living in the developing countries relies on traditional medicine for their healthcare needs.\(^5\) In India, such systems offer excellent remedies for gastrointestinal, cardiovascular and nervous disorders, tested through many centuries.\(^5,6\)

Analysis of natural medical substances in use in the medieval Levant showed 81.8% predominance of plant based substances.\(^6\) Although the complete mechanism of action of each remedy is lacking, again plant based phytotherapeutic agents represent
the majority used in medicine and most of these plant based substances have been shown to be effective at different stages of stone pathophysiology. Currently known extracts exert their antilithogenic properties by altering the ionic composition of urine, e.g. decreasing the calcium ion concentration or increasing magnesium and citrate excretion. These remedies can also express diuretic activity or they contain saponins that can disaggregate suspensions of mucoproteins, which are actually promoters of the crystallization process.

Cystone is a herbomineral formulation, designed and developed for the management of urolithiasis or renal calculi. This product came into existence in 1943 and since then this product has been in use all over the world for the management of urolithiasis and UTI. In studies conducted till date, Cystone has proven to be significantly effective (80%) in patients of urolithiasis.

In the present study, clinical trials and their details were tabulated and analyzed statistically. In case of all or none phenomenon (resolved and unresolved), Fisher’s exact test has been utilized. In case of within the group comparison (before and after drug therapy in the same patients), Student’s ‘t’ test has been employed. In case of comparison between different intervals, repeated measures of ANOVA test has been employed for meta-analysis. Statistical significance or statistical difference depends upon a number of factors including the population size. Some of the clinical trials of Cystone have a population size, which helps to make clear differentiation. On the other hand, there are some trials where study population of patients could have been more so that the statistical significance would have been achieved. None of the clinical trials were conducted to evaluate the relationship between Cystone’s efficacy, dose, and dosage regime.

The various studies of Cystone in urolithiasis can be broadly categorized into controlled and uncontrolled studies. The number of uncontrolled studies is definitely more as compared to controlled studies, especially the studies carried out before 1995. Non-randomized studies (controlled, uncontrolled, case reports and cross-sectional surveys) confirm the finding of a systematic review of randomized trials. They also provide information on long-term effects, prognostic factors, and adverse effects. While these may not be conclusive, they can provide useful summaries of the state of knowledge. However, efforts were made to document the efficacy of Cystone by averaging different clinical trials. Even in controlled studies, comparisons have been made with respect to different modalities like forced diuresis, antispasmodics, etc. The number of uncontrolled (open trial) and controlled trials of Cystone in urolithiasis was 23 and 8, in burning micturition it was 2 and 1, and in bacteuria/pus cells it was 6 and 5 respectively. The placebo-controlled clinical trials are very few. Nevertheless, an overview of these clinical trials indicates that Cystone is efficacious in the management of urolithiasis, especially when the site of urinary stone is ureter. The results obtained in urolithiasis are better as compared to nephrolithiasis. Few of the studies have evaluated the efficacy of Cystone in pediatric
population and stone formers. A study on pediatric urolithiasis, which was a double-blind placebo controlled study, involved 87 patients, the duration of treatment being 4 months. This study indicated significant symptomatic relief in patients of Cystone group along with significant reduction in 24-hour urinary excretion of calcium, magnesium, phosphorus, etc.

This analysis also indicates safety profile of Cystone. The adverse effects have been dyspepsia, flatulence and gastric irritation, which did not necessitate withdrawal of the drug. None of the studies have aimed to describe the mechanism of activity of Cystone.

Other studies have indicated the pharmacological activities of the ingredients of Cystone. Herbs like *Didymocarpus pedicellata* has been shown to have diuretic activity. Another plant, *Saxifraga ligulata*, is reported to have active principles like afzelechin and bergenin. Afzelechin and bergenin are tannins and possess astringent properties, which make them effective anti-microbial agents. Bergenin is a known diuretic and is helpful in dissolving kidney stones. The roots of *Rubia cordifolia* contain ruberythic acid, which has been proved to dissolve oxalate stones present in the urinary tract, thereby facilitating their expulsion without recourse to surgery. It also possesses astringent, antibacterial, and anti-inflammatory actions. The oil from the roots of *Cyperus scariosus* has been found to exhibit anti-inflammatory properties. Studies conducted on the extracts of *Cyperus scariosus* were found to have potent antioxidant activity. *Achyranthes aspera* has potent anti-inflammatory, astringent, demulcent, and diuretic activity. *Onosma bracteatum* is known to have diuretic action. It regulates urine output, acts as a demulcent, and provides soothing action. It is useful in bladder irritation and is a spasmylytic. *Hajrul Yahood bhasma* is useful as a diuretic and a lithotropic. It is given in retention of urine and in other diseases of the urinary tract. Shilajeet (purified) treats urinary disorders due to its tonic activity. It is probable that these ingredients may be producing an additive activity to bring about relief in urolithiasis.

In spite of large number of clinical trials conducted, a number of lacunae (few controlled trials and lack of dose dependent studies) still exist. These studies if carried out will go a long way in defining the role of Cystone in the management of urolithiasis.

**Conclusion**

The outcome of 50 clinical studies indicated that Cystone is useful in the management of Urolithiasis as revealed by the clearance of calculi, symptomatic relief, increased urine volume, and reduction in the stone forming constituents in urine with negligible adverse effects.
Acknowledgement
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