

Research Article

Evaluation of Efficacy and Safety of a Herbal Formulation Cystone Forte in the Management of Urolithiasis

Palaniyamma D^{1*}, and Jeyaraman R²¹Department of Clinical trial and Medical Services, The Himalaya Drug Company, Bangalore²Department of Urology, Sree Balaji Medical College & Hospital, Chennai

*Corresponding author

Palaniyamma D, Department of Clinical trial and Medical Services, The Himalaya Drug Company, Makali, 562 162, Bangalore, Tel: 91-8067549920; Email: dr.palani@himalayawellness.com

Submitted: 17 October 2017

Accepted: 28 November 2017

Published: 30 November 2017

ISSN: 2379-951X

Copyright

© 2017 Palaniyamma et al.

OPEN ACCESS

Keywords

• Urolithiasis; Renal Calculi; Cystone Forte; Hematuria; Micturition; Pain

Abstract

An open-label clinical study was conducted to evaluate the efficacy and safety of Cystone forte in the management of urolithiasis.

Sixty-five patients aged 18 to 50 years of either sex, with renal stones measuring > 5 mm and < 12 mm were included in the study. All the patients received Cystone forte at a dosage of 2 tablets BID for 3 months. In addition to calculi size, the patients were evaluated for amelioration of clinical symptoms such as colicky pain at the loin, pain in the abdomen, hematuria, dysuria, nausea/vomiting, pain on micturition, tenderness in kidney-urethra-bladder (KUB) area, fever/chills, and loss of appetite. Adverse events, if any, were recorded.

There was a significant decrease in the presence of renal calculi and calculi size from 6.82 ± 2.03 to 2.91 ± 2.31 mm ($p < .0001$) after treatment with Cystone forte. After the treatment, expulsion of renal calculi of > 5 to 6.9 mm was observed in 20 of 35 patients; expulsion of renal calculi of 7 to ≥ 12 mm was observed in 16 of 30 patients. The remaining patients displayed trend toward improvement of calculi-associated parameters.

There was a significant amelioration in other clinical symptoms after the treatment. No serious adverse effects were reported.

It can be concluded that Cystone forte is safe and effective in the management of urolithiasis.

ABBREVIATIONS

KUB: Kidney-Ureter-Bladder; Utis: Urinary Tract Infections

INTRODUCTION

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, such as hypercalciuria, hyperoxaluria, and cystinuria. Sometimes, urinary stones are formed because of chronic urinary tract infections (UTIs). Urinary stones can be calcium stones, cystine stones, uric acid stones, or struvite stones. They typically form inside the kidney (nephrolithiasis), ureter (urolithiasis), or urinary bladder. These calculi can vary in size and shape, and when they grow up to 2.3 mm, they obstruct 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 in conventional medical practice for dissolution or displacement of renal stones.

The incidence of urolithiasis is higher in developing countries (including India) than industrialized countries. It has been hypothesized that the main source of dietary proteins being cereals (unlike meat in Western countries) is an important etiological factor [1]. The northern and north-western regions of India can be described as an endemic stone-forming belt, due to a dietary pattern, rich in cereals and pulses [2].

Urolithiasis is a consequence of complex physiochemical processes, and the major contributory factors are urinary super saturation, crystallization, calculogenesis, and matrix formation. Calculogenesis is influenced by interplay of critical factors, such as stone inhibitors, complexing agents, and stone promoters. The sequence of events in the formation of any urinary stone can be urinary saturation[®] super saturation[®] nucleation[®] crystal growth[®] crystal aggregation[®] crystal retention[®] stone formation.

Kidney stones < 5 mm in diameter are most likely to be flushed out in urine without any medical intervention, except occasional analgesics and antispasmodics that enable the patient to endure the episode, which may last several days. Kidney stones > 5 mm in diameter are less likely to be flushed out in urine on their own and these stones get larger in size over a period of time. If the

kidney stone is > 10 mm in diameter, it has to be either removed by surgery or by lithotripsy.

Stones form twice as often in men as in women. The peak age at which stones form in men is 30 years, whereas women have a bimodal age distribution, with peaks at 35 and 55 years. The recurrence rate for urinary calculi is very high at approximately 50% [3].

The present study was conducted to evaluate the efficacy and safety of Cystone forte, a polyherbal formulation, in the management of urolithiasis. Each Cystone forte tablet comprises extracts of *Didymocarpus pedicellata*, *Saxifraga ligulata*, *Rubia cordifolia*, *Cyperus scariosus*, *Achyranthes aspera*, *Onosma bracteatum*, and *Vernonia cinerea*, and powders of purified Shilajeet and Hajrul yahood bhasma.

Aim

The aim of the study was to evaluate the efficacy and safety of Cystone forte in the management of urolithiasis, including bigger sized stones.

Materials and methods

Study design: This was an open-label clinical study of Cystone forte in the management of urolithiasis for 3 months.

Inclusion criteria: The patients with urolithiasis were included in the study. Patients were enquired for clinical symptoms such as colicky pain at the loin, pain in the abdomen, hematuria, dysuria, nausea/vomiting, pain during micturition, tenderness in kidney-ureter-bladder (KUB) area, fever/chills, and loss of appetite. Calculi size between > 5 and < 12 mm was measured ultrasonographically. The study patients aged between 18 and 50 years of either sex were included in the study. Only those who were willing to sign informed consent document and those who were ready to follow study procedures were included in the study.

Exclusion criteria: The patients with severe obstructive uropathy and serious systemic medical disorder and with a strong history of food or drug allergy of any kind were excluded. No other drugs (including aspirin) to be ingested during the course of the study. Pregnant and lactating women were not included in the study. Those who were unwilling to provide informed consent or abide by the requirements of the study were also excluded.

Study procedure: The study included 65 patients (36 men and 29 women) with renal stone disease. The patients with renal stones measuring > 5 and < 12 mm, presenting with or without symptoms such as dysuria, pain in the renal angle, and burning micturition were included in the study. Those with severe urinary tract infection, ureterohydronephrosis, diabetes, ulcer disease, history of hypersensitivity to herbal formulation, and pregnant women were excluded from the study. There was no dietary restriction per se, but the patients were advised not to consume oxalate-rich and calcium-rich diets.

The study protocol, informed consent form, case report form, and other study-related documents were approved by the local ethics committee. All the patients received Cystone forte at a

dosage of 2 tablets BID for 3 months. The patients were evaluated for amelioration of clinical symptoms such as colicky pain at the loin, pain in the abdomen, hematuria, dysuria, nausea/vomiting, pain on micturition, tenderness in KUB area, fever/chills, and loss of appetite in addition to the calculi size.

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 the patients, were recorded with information about severity, duration, and action taken regarding the study drug. Relation of adverse events with 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 end points:

1. To demonstrate the efficacy of Cystone forte tablet in the management of urolithiasis with rapid symptomatic recovery
2. To analyze the change from baseline values of clinical and laboratory parameters

Secondary end points:

1. To assess the safety profile of Cystone forte tablet in urolithiasis
2. To find out the incidence of adverse events during the study period, and overall compliance to the treatment

Statistical analysis

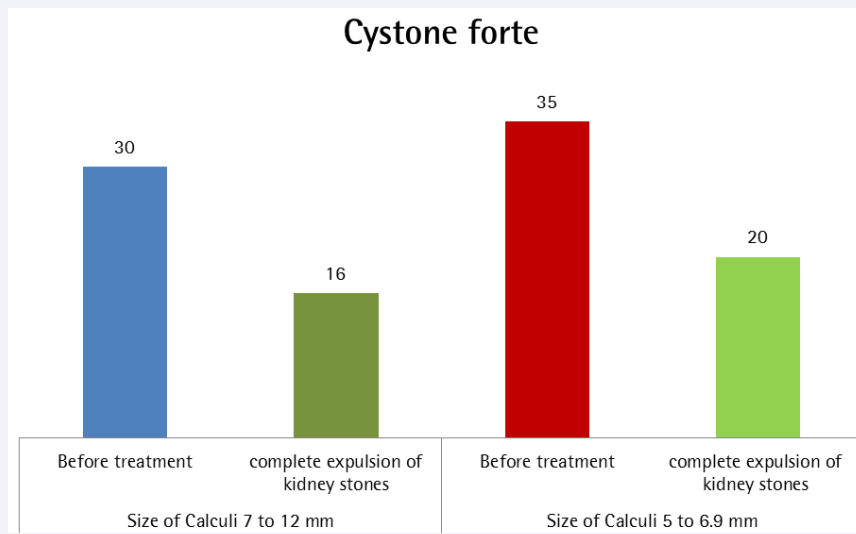
Statistical analysis was conducted according to intention-to-treat principles. Changes in various parameters from baseline values and values at the end of the study were pooled and analyzed using Fisher exact test and paired *t* test. Values are expressed as mean \pm SD or as incidences of patients with or without symptoms. The minimum level of significance was fixed at 95% confidence limit, and a 2-sided *p* value of < .05 was considered significant. Statistical analysis was performed using Graph Pad Prism software (version 6.07).

Results

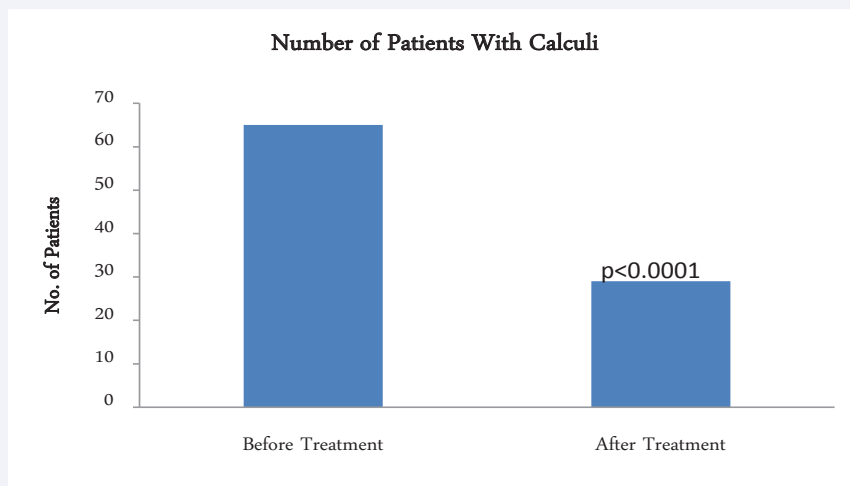
In this study, 65 patients of either sex were studied. The mean age range of patients included in all studies is 36.77 ± 10.74 years, and the duration of the treatment was 3 months (Table 1).

Data were available regarding the calculi size for 65 patients, and analysis of these data indicates that there was a significant decrease in presence of renal calculi (Table 2, Graph 3), and the calculi size decreased from 6.82 ± 2.03 to 2.91 ± 2.31 mm ($p < .0001$) after the treatment with Cystone forte. By the end of 1 month, about 6 patients reported that they felt the stone being expelled and were relieved of symptoms also.

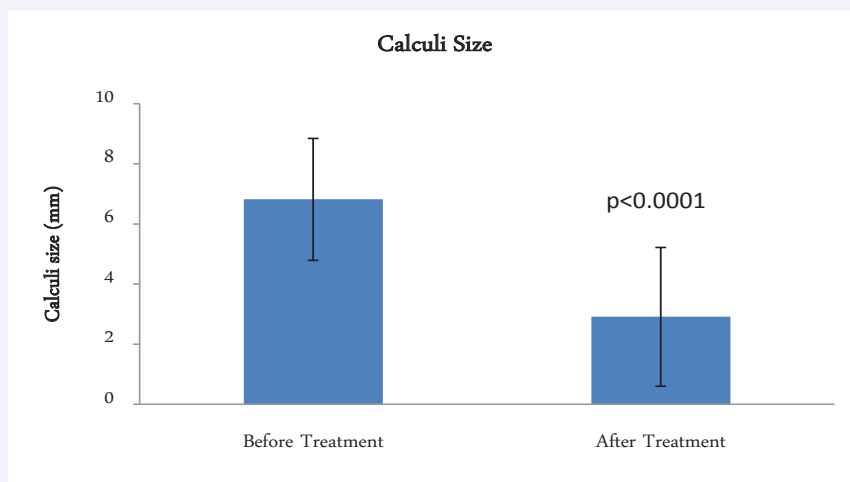
Of 65, 35 patients had renal calculi of > 5 to 6.9 mm; after the treatment, 20 patients expelled the stone with a significance of $p < .0001$. The remaining 30 patients had renal stone of 7 to ≥ 12



Graph 1 Expulsion of Calculi after Treatment with Cystone forte.



Graph 2 Number of Patients with Calculi.



Graph 3 Effect of Cystone forte on Clearance and Reduction of Calculi Size.

Table 1: Demographic Data with Dose and Duration of Cystone forte Treatment.

No. of Subjects	65
Sex (Male:Female)	36:29:00
Age, Mean \pm SD	36.77 \pm 10.74
Duration of Treatment	3 Months

Table 2: Effect of Cystone forte on Clearance of Calculi and on Reduction of Calculi Size.

Parameters	Before Treatment	After Treatment	p Values
Number of Patients With Calculi	65	29	< .0001
Calculi Size,* Mean \pm SD	6.82 \pm 2.03	2.91 \pm 2.31	< .0001

Statistical analysis: Fisher exact test to study the presence of calculi and paired *t* test to study the calculi size.

Table 3: Expulsion of Calculi after Treatment with Cystone forte.

Category	Before Treatment, n	After Treatment, n	p Values
> 5 to 6.9, mm	35	20	< .0001
7 to \geq 12, mm	30	16	< .0001

Statistical analysis: Fisher exact test.

Table 4: Evaluation of Clinical Parameters on Treatment with Cystone forte Tablet.

Parameters	Before Treatment	After Treatment	p Values
Colicky Pain at the Loin	31	4	< .0001
Pain in the Abdomen	40	21	< .0002
Hematuria	13	1	< .0012
Dysuria	49	16	< .0001
Nausea/Vomiting	18	0	< .0001
Pain on Micturition	31	15	< .0024
Tenderness in KUB Area	7	6	NS
Fever/Chills	6	2	NS
Loss of Appetite	14	1	< .0004

Statistical analysis: Fisher exact test.
 KUB, kidney-ureter-bladder; NS, not significant.

Table 5: Overall Impression.

Scale	By the Patients, %	By the Investigators, %
Cured = 1	36.71	54.43
Marked Improvement = 2	16.46	6.33
Moderate Improvement = 3	18.99	13.92
Slight Improvement = 4	16.46	10.13
No Change = 5	10.13	13.92
Symptoms Became Worse = 6	1.27	1.27

above and 16 patients among these expelled the stone completely with a significance of $p < .0001$ after the treatment. Other patients showed a trend of significant improvement in the reduction of renal calculi (Table 3, Graph 1, Graph 2).

The statistical analysis also indicates that Cystone forte brings about significant relief in all the clinical symptoms studied (Table 4, Graph 4).

Colicky pain at the loin was present in 31 patients, and after the treatment, only 4 patients showed the symptom with a significance of $p < .0001$. Pain in the abdomen was present in 40 patients, and at the end of the study, only 21 showed the symptom with a significance of $p < .0002$. Hematuria was present in 13 patients, and at the end of the study, 12 patients got cured with only 1 showing the symptom with a significance of $p < .0012$.

Dysuria was present in 49 patients, and after the treatment, 16 patients had the symptom with a significance of $p < .0001$. Nausea/vomiting was present in 18 patients, but was cured in all the patients with a significance of $p < .0001$.

Pain on micturition was present in 31 patients, and after the treatment, 15 patients had the symptom with a significance of $p < .0024$. Six patients experienced fever/chills, and after the treatment, 4 patients were relieved. Loss of appetite was seen in 14 patients, which was relieved in 13 patients with a significance of $p < .0004$.

Adverse effects: Sixty-five patients had received Cystone forte at a dosage of 2 tablets BID for 3 months. No serious adverse effects were noted in the study patients; hence none withdrew from the study.

Overall impression was assessed by both the investigator and the patients after the treatment (Table 5, Graph 5). In the study group, 36.71% of patients showed complete cure; 16.46% showed a marked improvement; 18.99% showed moderate improvement; and 16.46% showed slight improvement, as observed by the patients.

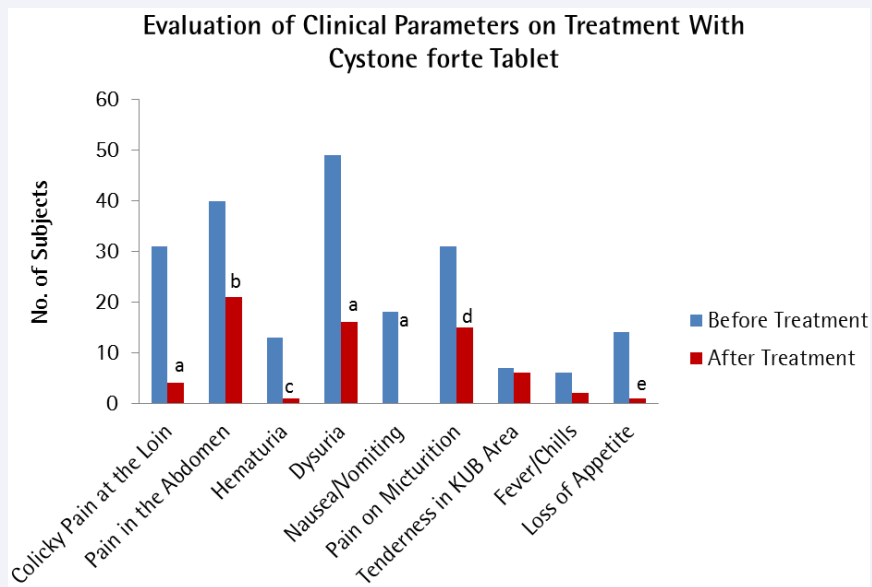
In the study group, 54.43% of patients showed complete cure; 6.33% showed marked improvement; 13.92% showed moderate improvement; and 10.13% showed slight improvement, as observed by the investigators.

Hence, the study concludes that Cystone forte is safe and effective in the treatment of urolithiasis, with significant improvement in clinical symptoms—the clearance of calculi, symptomatic relief, and increased urine volume. No adverse effects were observed or reported during the clinical study.

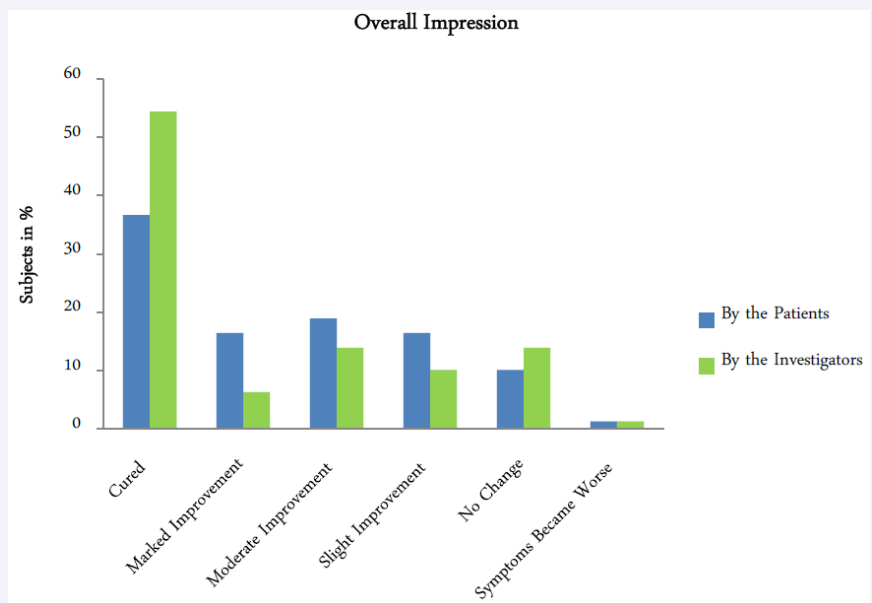
DISCUSSION

Urolithiasis is an age-old disease. Stones in the urinary tract are known to have been present even in the ancient people thousands of years ago. However, the incidence of the disease varies in different parts of the world. Urinary stones occur in people of all socioeconomic groups. The calculi are equally common in executives, athletes, laborers, students, and others. Urinary calculi may or may not produce clinical symptoms.

Many theories have been proposed to explain the mechanism of stone formation, but none has satisfactorily accounted for all



Graph 4 Evaluation of Clinical Parameters.
 a: $p < 0.0001$, b: $p < 0.0002$, c: $p < 0.0012$, d: $p < 0.0024$, e: $p < 0.0004$



Graph 5 Overall Impression.

the aspects of the problem. In humans, urinary calculi consist of crystalloid deposits in or on to the organic matrix [4].

The high incidence along with remarkable recurrence rates makes urolithiasis a serious social and economical problem for the society. Although the symptoms and consequences are not life threatening in majority of patients, stones in the urinary tract form a major cause of morbidity, hospitalization, and days lost from work [5]

Urinary stones are polycrystalline concretions that occur in the urinary tract of humans and animals. Like bones and teeth, they are biominerals. While the nonpathological products of

biomineralization, formed in genetically determined processes, display a high degree of biological organization, uroliths are a special case. Their formation is governed by pathoanatomical and physicochemical factors [6]. Around 97% of urinary stones are found in the kidneys and ureters (kidney stones), the remaining 3% in the urinary bladder and urethra [7].

Urinary stones can range in size from micrometers to several centimeters in diameter. They frequently remain unnoticed for a long period before manifesting themselves—often very painfully—or being discovered incidentally on radiography or ultrasound.

The most commonly occurring leading symptom is radiating colicky pain in the hypochondrium. The pain varies depending on the position of the stone in the ureter and may attain excruciating intensity [8].

Cystone forte is a herbomineral formulation, designed and developed for the management of urolithiasis or renal calculi. This analysis also indicates safety profile of Cystone forte. The adverse effects have been dyspepsia, flatulence and gastric irritation, which did not necessitate withdrawal of the drug.

The literature evidences pharmacological properties of the ingredients of Cystone forte. *Didymocarpus pedicellata* has been known to exhibit diuretic activity [9]. *Saxifraga ligulata* is reported to have active principles such as afzelechin and bergenin. Both are tannins and possess astringent property, which makes them effective antimicrobial agents. Bergenin is a known diuretic and is helpful in dissolving kidney stones [10,11]. The roots of *Rubia cordifolia* contain ruberythric acid, which has been proved to dissolve oxalate stones present in the urinary tract, thereby facilitating their expulsion without recourse to surgery [12-14]. It also possesses astringent, antibacterial, and anti-inflammatory properties. The oil from the roots of *Cyperus scariosus* has been found to exhibit anti-inflammatory properties [15,16]. Studies conducted on the extracts of *C. scariosus* have proved their potent antioxidant activity. *Achyranthes aspera* has potent anti-inflammatory, astringent, demulcent, and diuretic properties [17]. *Onosma bracteatum* is known to have diuretic property. It regulates urine output, acts as a demulcent, and provides soothing action. It reduces bladder irritation and acts as a spasmolytic agent [18]. Hajrul Yahood bhasma [19] acts as a diuretic and a lithotropic agent. It helps reduce retention of urine and is also used to treat other diseases of the urinary tract. Shilajeet (purified) helps treat urinary disorders because of its tonic activity [20]. The efficacy of Cystone forte can be attributed to synergistic activity of all these herbs present in the formulation in the treatment of urolithiasis.

CONCLUSION

The study results indicate that the polyherbal formulation, Cystone forte, is safe and effective in the treatment of urolithiasis, with significant improvement in clinical symptoms—the clearance of calculi, symptomatic relief, and increased urine volume. No adverse effects were observed or reported during the clinical study. Cystone forte is effective and safe in the long-term treatment of urolithiasis. Additionally, it is also found to

be beneficial in expelling and/or reducing the size of the renal stones, including bigger-sized stones ranging from 7 to 12 mm.

REFERENCES

1. Polinsky MS, et al. *Pediatr Clin North Am.* 1987; 3: 683–704.
2. Teotia M, et al. *Postgraduate Med.* 1977; 53: 41–48.
3. Butterweck V, et al. *Planta Med.* 2009; 75: 1095–1103.
4. Koyuncu HH, Faruk Yencilek, Bilal Eryildirim, Kemal Sarica. Family history in stone disease: how important is it for the onset of the disease and the incidence of recurrence?. *Urol Res.* 2010; 38: 105-109.
5. Stamatelou KK, Francis ME, Jones CA, Nyberg LM, Curhan GC. Time trends in reported prevalence of kidney stones in the United States: 1976-1994. *Kidney Int.* 2003; 63: 1817–1823.
6. Hesse A. *Harnsteine.* Stuttgart: Thieme Verlag. 1982.
7. Bichler K. *Epidemiologie.* In: Bichler K, ed. *Das Harnsteinleiden.* GEK-Edition. Lehmanns Media – LOB.de; 2007; 52: 31–44.
8. Hautmann R, et al. eds. *Urologie.* 5th revised edition. Springer; 2014.
9. Linde K, et al. *J Clin Epidemiol.* 2002;55(1):77–85.
10. Asolkar LV, Chopra RN, Nayar SL, Chopra IC, Kakkar KK, et al. *Saxifraga ligulata.* Glossary of Indian Medicinal plants with Active Principles (Second supplement), Part I (A–K). New Delhi: CSIR Publication. 1992: 122.
11. Chopra RN, et al. *Saxifraga ligulata.* Glossary of Indian Medicinal Plants. New Delhi: National Institute of Science Communication. 1996: 223.
12. Basu S. *Phytother Res.* 2006; 20: 896–900.
13. Tripathi YB. *Phytomed.* 1999; 6: 51–57.
14. Joy J. *J Cancer Res Ther.* 2008; 4: 111–115.
15. Chopra RN. *Cyperus scariosus.* Glossary of Indian Medicinal Plants. New Delhi: National Institute of Science Communication. 1996: 89.
16. Khare CP. *Indian Medicinal Plants: An Illustrated Dictionary.* Springer. 2004; 195–196.
17. Chopra RN. *Achyranthes aspera.* Glossary of Indian Medicinal Plants. New Delhi: National Institute of Science Communication; 1996: 4.
18. Khare CP. *Encyclopedia of Indian Medicinal Plants.* Springer. 2007: 337–338.
19. Anonymous. *Ayurveda Sarsangraha.* Hajrul Yahood bhasma. Allahabad: Shree Baidyanath Ayurved Bhavan Ltd. 1996: 175–176.
20. Mookerjee B. *Shilajeet. Rasa Jala Nidhi.* Vol. II. Varanasi, India: Srigokul Mudranalaya. 1980: 89–91.

Cite this article

Palaniyamma D, Jeyaraman R (2017) Evaluation of Efficacy and Safety of a Herbal Formulation Cystone Forte in the Management of Urolithiasis. *J Urol Res* 4(4): 1093.