Available online at www.sciencedirect.com
ScienceDirect
European Journal of Integrative Medicine 3 (2011) 23–28
European Journal of INTEGRATIVE MEDICINE
www.elsevier.com/eujim

Original article

Evaluation of an Ayurvedic formulation (Cystone), in urolithiasis: A double blind, placebo-controlled study

M.G. Shekar Kumaran [a], Pralhad S. Patki [b,*]

[a] *Shree Sai Hospitals, Choolaimedu, Chennai, India*
[b] *Head-Medical Services and Clinical Trials, R&D Center, The Himalaya Drug Company, Bangalore, India*

Received 25 May 2010; received in revised form 3 November 2010; accepted 4 February 2011

Abstract

Aim of the study: To evaluate the safety and efficacy of Ayurvedic formulation in patients with urolithiasis by assessing the symptomatic relief, reduction/expulsion of renal stones, urinary biochemical parameters.
Materials and methods: In this study, 60 patients with renal calculi size between 5 mm and 12 mm were included. Thirty patients received Ayurvedic formulation and remaining 30 received placebo orally in a dose of 2 tablets twice daily for 12 weeks. Patients were evaluated at 6 and 12 weeks for relief of clinical symptoms as well as urine and biochemical parameters. X-ray (KUB) and an ultrasound examination were carried out on entry, 6 weeks, 12 weeks of the study.
Results: The Ayurvedic formulation helped in expulsion of stones in 18 patients (66.7%) {placebo 3 (10%)}. The average time for expulsion was 12.3 days (range 7–20) in patients treated with Ayurvedic formulation with a significant reduction in the calculi size, whereas there was no decrease in the size of the stone in patients treated with placebo. There were improvement in clinical symptoms and hematuria, frequency of urination, and tenderness in KUB area. Significant reduction in the number of urinary RBC and WBC was observed in patients on Ayurvedic formulation along with significant decrease in serum uric acid levels.
Conclusions: This Ayurvedic formulation appears to be safe and beneficial in patients who have smaller renal stones. It increases the stone expulsion rate.

Keywords: Urinary calculi; Ayurvedic formulation; Urolithiasis

Introduction

Stone formation in kidney is one of the oldest and the most widespread medical afflictions known to humans. Urinary calculi have been found in Egyptian mummies dating back to 4000 BC and in the remains of 1500–1000 BC old North American Indians. Reference to stone formation is also made in early Sanskrit documents from India between 3000 and 2000 BC [1]. Kidney stones affect up to 5% of the population, with a lifetime risk of passing a kidney stone of about 8–10% [2]. Increased incidence of kidney stones in the industrialized world is associated with improved standards of living and is strongly associated with race or ethnicity and region of residence [3]. Stones form twice as often in men as in women. The peak age in men is 30 years; 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% [4].

In the United States, urolithiasis is associated with a significant medical expenditure exceeding 1.5 billion dollars annually [5].

The process of stone formation depends on urinary volume; concentrations of calcium, phosphate, oxalate, sodium, and uric acid ions; concentrations of natural calculi inhibitors (e.g. citrate, magnesium, Tamm-Horsfall mucoproteins, bikunin); and urinary pH [6]. Calculi are classified into five categories based on their composition: calcium oxalate (70%), calcium phosphate (5–10%), uric acid (10%), struvite (15–20%), and cystine (1%) [1].

The classic presentation for a patient with renal colic is acute loin to groin colicky pain associated with nausea and vomiting. These symptoms combined with renal angle tenderness and microscopic hematuria are highly predictive of urinary tract

* Corresponding author. Tel.: +91 80 2371 4444; fax: +91 80 2371 4472.
E-mail address: dr.patki@himalayahealthcare.com (P.S. Patki).

1876-3820/$ – see front matter © 2011 Elsevier GmbH. All rights reserved.
doi:10.1016/j.eujim.2011.02.003

stone disease with a sensitivity of 84% and a specificity of 99%. One third of incidental stones may become symptomatic [7].

With hydration and pain control, calculi smaller than 5 mm pass spontaneously in approximately 90% of patients. The rate of stone passage decreases as the stone size increases; a 10 mm stone has <10% chance of passing without surgical intervention [8]. Recent studies have suggested that the use of α_1-adrenergic blocker, tamsulosin, may increase the chance of spontaneous passage of ureteric calculi [9].

The efficacy of invasive therapies, such as extracorporeal shock wave lithotripsy and ureteroscopy, has been proven by several studies [8,10]. Nevertheless, these techniques are not risk-free, are problematic, and quite expensive [11]. Moreover, even the simple wait and watch approach can result in complications, such as infection of the urinary tract, hydronephrosis, and can affect the renal functions [12].

Recent studies have shown that the use of phytotherapy along with the watchful waiting approach can reduce the symptoms of urolithiasis and facilitate stone expulsion [3,13]. In the present study, an Ayurvedic preparation claimed to be effective in the treatment of urolithiasis, is evaluated for its safety and efficacy in a randomized, double blind, placebo-controlled design. The principal herbs of the Ayurvedic tablets include extracts of *Didymocarpus pedicellata*, *Saxifraga lingulata*, *Rubia cordifolia*, *Cyperus scariosus*, *Achyranthes aspera*, *Onosma bracteatum*, and *Vernonia cineria* and are claimed to reduce the size of urinary stones and facilitate the expulsion of stones formed in the body. This formulation has been approved by regulatory authorities in India.

Materials and methods

The study included 60 patients with renal stone disease (39 males and 21 females) seen from October 2008 to December 2009 at the Urology Clinic, Shree Sai Hospitals, Chennai. Renal stones were diagnosed by X-ray kidney, ureter and bladder (KUB) and ultrasonography. Patients with renal stones greater than 5 mm in size but <12 mm, presenting with or without symptoms such as dysuria, pain in the renal angle or flanks radiating to the groin, and burning micturition were included in the study. Subjects with severe urinary tract infection, uretero-hydronephrosis, diabetes, ulcer disease, history of hypersensitivity to herbal formulation, and pregnant women were excluded from the study. There were no dietary restriction per se, but the patients were advised not to take oxalate rich and calcium rich diet.

The study protocol, informed consent form, case report form, and other study-related documents were approved by the local ethics committee.

A total of 60 patients were randomly divided into two groups of 30 each in a randomized double-blind placebo-controlled design. The sample size and randomization were done by computer generated statistical programme. All the patients received either 2 tablets of Ayurvedic formulation or identical looking placebo, at a dose of 2 tablets twice daily for a period of 12 weeks.

All patients were allowed to use symptomatic therapy with pain killers, if required and were advised to drink a minimum of 2 l of water daily. The follow up was limited to 12 weeks. All patients were examined at 6th and 12th week clinically and by X-ray (KUB) and ultrasonography. Patients were evaluated for amelioration in the relief of clinical symptoms like pain in the abdomen, number of pain episodes, frequency of urination, dysuria, hematuria, painful micturition, and tenderness in KUB area at entry, 6 weeks, and 12 weeks. All the parameters except number of pain episodes and frequency of urination were evaluated using a 4-point grading scale (0: normal; 1: mild; 2: moderate; and 3: severe). In addition urine analysis (pH, microscopical evaluation of RBC and WBC) and hematological and biochemical parameters (renal function test and electrolytes) were evaluated at entry and at the end of the study (12 weeks). Adverse effects of the therapy, if any, were also recorded during the follow-up visits. Evaluation was carried out for calculi size, expulsion rate, total expulsion of calculi, and the amount of analgesic consumed.

Adverse events

All adverse events, either reported or observed by patients, were recorded with information about severity, date of onset, duration, and action taken regarding the study drug. Relation of adverse events to the study medication was predefined as "Unrelated" (follows 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).

Patients were allowed to voluntarily withdraw from the study, if they so desired without assigning reasons. For patients withdrawing from the study, efforts were made to ascertain the reason for dropout. Non compliance (defined as failure to take <80% of the medication) was not regarded as treatment failure, and reasons for non compliance were noted.

Statistical analysis

Statistical analysis was performed using Graphpad Prism version 4.03, for windows (Graphpad software, San Diego, CA, USA) by repeated measures of ANOVA (Friedman test) followed by Dunnett's multiple comparison post hoc test for the presence or absence of various signs and symptoms of urolithiasis. Urinary parameters and calculi size were analyzed by Wilcoxon signed-rank test, biochemical parameters by paired '*t*'-test and complete expulsion of calculi by Fisher's exact test. Values were expressed as mean ± SD for calculi size, relief of clinical symptoms, urine, and biochemical parameters. Complete expulsion of renal stones was expressed as the incidence of occurrences in placebo and Ayurvedic formulation treated groups. The minimum level of significance was fixed at $p < 0.05$.

Results

Ayurvedic formulation group consisted of 20 men and 10 women (average age 33.6 ± 11.4 years) and placebo group consisted of 19 men and 11 women (30.5 ± 14.2 years). Average stone size was 8.30 ± 2.58 mm in Ayurvedic formulation group and 8.8 ± 2.9 mm for placebo group (Table 1).

Expulsion of stones was observed in 18 patients (66.7%) on Ayurvedic therapy with a significance of $p < 0.0006$, whereas in placebo group, expulsion of stones was observed in only 3 patients (10%) (Table 2).

The average time for expulsion was 12.3 days (range 7–20) in Ayurvedic formulation group and 17.9 days (range 15–22) in placebo group. No significant differences were observed in the expulsion rates between males and females and between right and left sides.

The study showed significant reduction in the calculi size from 8.30 ± 2.58 mm to 5.60 ± 4.95 mm at the end of the treatment, in patients treated with Ayurvedic formulation ($p < 0.0014$). No decrease in the size of the stone was observed in patients treated with placebo (Table 3).

In patients treated with Ayurvedic formulation, significant improvement was observed in clinical symptoms such as pain in abdomen, number of pain episodes, dysuria, and painful micturition. A decreasing trend was also observed in other parameters such as frequency of urination, hematuria, and tenderness in KUB area, but was not found to be significant (Table 4).

Urine microscopy revealed a significant reduction in the number of RBCs ($p < 0.027$) and WBCs ($p < 0.048$) in the patients treated with Ayurvedic formulation. No significant differences were observed in both parameters in the placebo group (Table 5). Biochemical investigations showed a significant decrease in the uric acid values as compared to on-entry values inpatients of Ayurvedic formulation group. Other parameters were also found to be within the normal range. No significant changes were observed for any of these parameters in patients treated with placebo (Table 6).

No adverse drug effects were either reported or observed during the entire study period except for two episodes of vomiting in one patient, gastric irritation in one, and dyspepsia in one patient in Ayurvedic formulation treated group, which did not necessitate the withdrawal of the drug. Likewise solitary incidence of gastric irritation was observed in the placebo group. Four patients in placebo group, discontinued the treatment, and minimal invasive methods were carried out for the expulsion of stones.

Table 1
Demographic data of patients on entry.

Parameters	Ayurvedic formulation ($n = 30$)	Placebo ($n = 30$)
Mean age (in years)	33.6 ± 11.4	30.5 ± 14.2
Male:female	20:10	19:11
Smokers	10	12
Alcoholics	6	4
Diet (veg:nonveg)	13:17	20:10
Average size of the stone (mm)	8.30 ± 2.58	8.80 ± 2.90

Table 2
Effect of drug treatment on renal stones.

Group	Time of assessment	No. of patients	
		Present	Absent
Ayurvedic formulation	Before treatment	30	0
	After treatment	12	18*
Placebo	Before treatment	30	0
	After treatment	27	3

Statistical analysis was carried out using Fisher's exact test.
* $p < 0.0006$ as compared with "Before treatment" values.

Table 3
Effect of drug treatment on mean calculi size (mm) (mean ± SD).

Group	Before treatment	After treatment
Ayurvedic formulation	8.30 ± 2.58	5.60 ± 1.95*
Placebo	8.82 ± 2.92	8.89 ± 3.66

Statistical analysis was carried out by paired "*t*" test.
* $p < 0.0014$ as compared with "Before treatment" values.

Discussion

Urolithiasis is a complex process that results from a succession of several physicochemical events including supersaturation, nucleation, growth, aggregation and retention within the kidneys. Treatment of urolithiasis involves either conventional therapy or interventional procedures. The primary agents in medical management for urolithiasis, has been investigated with calcium channel blockers, steroids, nonsteroidal anti-inflammatory drugs (NSAIDs), and α_1-adrenergic receptor antagonists [14]. Although calcium channel blockers with or without steroids and/or NSAIDs have shown to be successful in the treatment, α-blockers, with their high success rates have become the leading candidate in medical therapy [15]. However, these treatment regimens are not free from side effects.

The endoscopic stone management have allowed kidney stones to be treated using minimally invasive techniques, which have increased success rates and decreased treatment-related morbidity. These advances include shock wave lithotripsy (SWL), ureteroscopy, and percutaneous nephrostolithotomy. Although these approaches are less invasive than the traditional open surgical approaches, they are expensive and have inherent risks [8].

Due to the high cost and adverse effects of minimally invasive techniques, and recurrence alternative treatment modalities with phytotherapeutic agents have become the mainstay of medical therapy. In the present study, an Ayurvedic formulation containing principal herbs useful in the treatment of urinary calculi, was evaluated for its safety and efficacy. Effect of oral administration of Cystone on calcium oxalate lithiasis in rats using glycolic acid experimental model was studied and was found to prevent the urinary supersaturation of lithogenic substances [16]. Levels of urinary supersaturation correlate with the type of stone formed, and lowering of supersaturation is effective

Table 4
Changes in mean clinical symptom score on treatment with Ayurvedic formulation/placebo (mean ± SD).

Clinical symptoms	Ayurvedic formulation			Placebo		
	Day 0	6 weeks	12 weeks	Day 0	6 weeks	12 weeks
Abdominal pain	2.36 ± 0.56	1.36 ± 0.76 [a]$p < 0.001$ [b]$p < 0.01$	1.00 ± 0.87 [a,b]$p < 0.001$	2.88 ± 0.78	2.55 ± 0.62	2.67 ± 0.84
No. of pain episodes	2.72 ± 1.34	1.52 ± 0.71 [a]$p < 0.01$	0.92 ± 0.86 [a,b]$p < 0.001$	2.77 ± 1.89	2.34 ± 1.57	2.78 ± 1.74
Urinary frequency (day)	5.40 ± 1.68	4.76 ± 1.20	4.72 ± 0.93	5.99 ± 1.74	5.99 ± 1.60	5.67 ± 1.90
Urinary frequency (night)	1.64 ± 0.76	1.24 ± 0.66	1.24 ± 0.52	1.57 ± 0.88	1.89 ± 0.08	1.78 ± 0.02
Dysuria	1.12 ± 1.17	0.64 ± 0.86	0.44 ± 0.71 [a,b]$p < 0.005$	1.98 ± 1.56	1.23 ± 1.77	1.67 ± 1.89
Hematuria	0.12 ± 0.33	0.00 ± 0.00	0.00 ± 0.00	0.450 ± 0.73	0.027 ± 0.99	0.012 ± 0.77
Painful micturition	1.0 ± 1.12	0.52 ± 0.77	0.32 ± 0.48 [a,b]$p < 0.05$	2.0 ± 1.12	2.40 ± 1.62	2.90 ± 1.99
Tenderness in KUB area	0.52 ± 0.92	0.36 ± 0.76	0.24 ± 0.72	0.80 ± 0.91	0.80 ± 0.64	0.70 ± 0.79

Statistical analysis was carried out using repeated measures of ANOVA by Friedman test followed by Dunnett's multiple comparison test.
[a] As compared to Day 0.
[b] As compared to 6 week value.

Table 5
Effect of drug treatment on urinary parameters.

Parameter	Ayurvedic formulation		Placebo	
	Day 0	Week 12	Day 0	Week 12
Urine pH	6.05 ± 0.36	5.96 ± 0.30	6.12 ± 0.66	5.99 ± 1.66
No. of RBCs per HPF	2.08 ± 2.64	1.50 ± 2.15 ($p < 0.027$)	2.47 ± 2.95	2.17 ± 2.88
No. of WBCs per HPF	2.88 ± 2.06	2.13 ± 1.45 ($p < 0.048$)	2.89 ± 2.06	2.14 ± 2.78

Mean ± SD, statistical analysis performed using Wilcoxon signed-rank test.
Note: p value as compared to "Day 0" values.

for preventing stone recurrence and reduces the relapse risk [3]. In vitro crystallization systems are widely used to study the processes of crystal nucleation growth and agglomeration, which in turn helps in exploring the pathophysiology of renal stone disease. In vitro and in vivo studies on crystallization showed an inhibition of the matrix bound mineral phase formation and its subsequent growth with the Cystone [17,18]. The findings of the study showed beneficial effects of Ayurvedic formulation (Cystone) as revealed by the improvement of various clinical symptoms, increased stone expulsion rate and the time required for expulsion as well as urine microscopy (WBC and RBC), which correlated well with the experimental findings.

In addition to the prevention of urinary supersaturation, it is also established that reactive oxygen species is also responsible for cellular injury; therefore, a reduction in renal oxidative stress could be another effective therapeutic approach in the treatment of urolithiasis. Experimental study of Cystone in cisplatin-induced nephrotoxicity inhibited the lipid peroxidation in the renal cortical slices. This property of Cystone could help in normal function by preventing the cellular injury [19].

The beneficial actions of Ayurvedic formulation (Cystone) could be due to the complex spectrum of actions including anti-inflammatory, antimicrobial, diuretic, antispasmodic, litholytic, and anticalcifying activities of its ingredients. *D. pedicellata*

Table 6
Effect of drug treatment on biochemical parameters.

Parameters	Ayurvedic formulation		Placebo	
	Day 0	Week 12	Day 0	Week 12
Blood urea (mg/dl)	24.48 ± 4.67	24.36 ± 3.26	22.48 ± 4.45	20.48 ± 4.45
Creatinine (mg/dl)	0.90 ± 0.10	0.87 ± 0.11	0.94 ± 0.16	0.88 ± 0.18
Sodium (mEq/l)	134.7 ± 11.94	134.8 ± 9.65	128.9 ± 10.82	127.4 ± 12.77
Potassium (mEq/l)	3.96 ± 0.52	4.04 ± 0.31	3.66 ± 0.76	3.03 ± 0.35
Calcium (mg/dl)	9.43 ± 0.85	9.36 ± 0.63	9.90 ± 0.46	9.78 ± 0.76
Bicarbonate (mEq/l)	25.08 ± 3.14	24.60 ± 3.71	25.27 ± 3.67	25.88 ± 3.33
Uric acid (mg/dl)	4.16 ± 0.72	3.92 ± 0.55 ($p < 0.0221$)	4.79 ± 0.06	4.77 ± 0.86

Mean ± SD, statistical analysis: paired t-test.
Note: p value as compared to "Day 0" values.

has been found to exhibit diuretic activity [20]. *S. lingulata*, is reported to have active principles such as bergenin and afzelechin that possess astringent properties, making it an effective antimicrobial agent. Bergenin is a known diuretic and is established to be effective in glycolic acid-induced urolithiasis as well as in the inhibition of growth of urinary crystals by acting on the crystalloid-colloid balance [21–23]. *R. cordifolia* is found to exhibit anti-inflammatory activity as well as dose dependent increase in urine volume and electrolyte excretion [24,25]. *C. scariosus* is reported to inhibit histamine and acetylcholine-induced contraction of guinea pig ileum indicating nonspecific spasmolytic action [26]. Effect of *A. aspera* on inhibition of mineralization of urinary stone forming minerals using four models that included simultaneous flow static model, simultaneous flow dynamic model, reservoir static model and reservoir dynamic model and the results revealed inhibition of mineralization [27]. *O. bracteatum* is reported diuretic and spasmolytic action [28]. *V. cineria* is reported in the literature for its anti-inflammatory, analgesic and antibacterial properties [29,30].

The observed beneficial effects in the management of urolithiasis following an Ayurvedic formulation treatment in this trial could be due to the prevention of urinary supersaturation, inhibition of mineralization of stone-forming constituents, normalization of cellular function in renal oxidative stress, correction of crystalloid-colloid balance as well as the beneficial effects such as anti-inflammatory, antimicrobial, diuretic, antispasmodic, litholytic, and anticalcifying activities of individual ingredients. Study involving larger population of patients will be necessary to confirm the findings of this study. Urolithiasis (*Mutrashmari*) in Ayurveda is described as a painful disease which needs to be addressed early. In the beginning stages, disease can be effectively managed with medical intervention, while in the later stages with enlarged stones, the only successful measure would be lithotripsy. The medical management would include the administration of lithotriptic herbs and substances besides the measures to manage the bio-energies that control the disease manifestations. With this line of treatment, Ayurveda envisages that the stone forming substances are controlled, which prevents recurrence of the stone [31]. Ayurvedic recommendations on diet and seasonal routine cannot be tested in a double blind placebo controlled study.

Conclusion

The results of the present study indicated that the Ayurvedic formulation (Cystone) is safe and effective in the treatment of urolithiasis, with significant improvement in symptoms associated with renal stones. This Ayurvedic formulation has also shown to facilitate stone expulsion rate. It has significantly reduced concomitant symptomatic treatment with pain killers. Hence, this Ayurvedic formulation appears to be an effective and safe phytotherapeutic agent and could be useful in the alternative management of urolithiasis.

Conflict of interest

No conflict of interest declared.

References

[1] Patankar S, Dobhada S, Bhansali M, Khaladkar S, Modi J. A prospective, randomized, controlled study to evaluate the efficacy and tolerability of Ayurvedic formulation “varuna and banana stem” in the management of urinary stones. J Altern Complement Med 2008;14(10):1287–90.

[2] Asplin JR, Favus MJ, Coe FL. Nephrolithiasis. In: Brenner BM, editor. Brenner and Rector’s the kidney. 5th ed. Philadelphia: Saunders; 1996. p. 1893–935.

[3] Butterweck V, Khan SR. Herbal medicines in the management of urolithiasis: alternative or complementary? Planta Med 2009;75(10):1095–103.

[4] Sutherland JW, Parks JH, Coe FL. Recurrence after a single renal stone in a community practice. Miner Electrolyte Metab 1985;11:267–9.

[5] Schwartz BF, Schenkman N, Nguyen R, Stollerc ML. Gahat. A Nepalese cure for urolithiasis? Urol 2000;56(6):912–4.

[6] Menon M, Resnick MI. Urinary lithiasis: etiology, diagnosis, and medical management. In: Campbell MF, Walsh PC, Retik AB, editors. Campbell’s urology. 8th ed. Philadelphia: Saunders; 2002. p. 3230–437.

[7] Eskelinen M, Ikonen J, Lipponen P. Usefulness of history-taking, physical examination and diagnostic scoring in acute renal colic. Eur J Urol 1998;34:467–73.

[8] Segura JW, Preminger GM, Assimos DG, Dretler SP, Kahn RI, Lingeman JE, et al. Ureteral Stones Clinical Guidelines Panel summary report on the management of ureteral calculi. J Urol 1997;158(5):1915–21.

[9] Porpiglia F, Ghignone G, Fiori C, Fontana D, Scarpa RM. Nifedipine versus tamsulosin for the management of lower ureteral stones. J Urol 2004;172(2):568–71.

[10] Miller OF, Kane CJ. Time to stone passage for observed ureteral calculi: a guide for patient education. J Urol 1999;162:690–1.

[11] Lotan Y, Gettman MT, Roehrborn CG, Cadeddu JA, Pearle MS. Management of ureteral calculi: a cost comparison and decision making analysis. J Urol 2002;167(4):1621–9.

[12] Ueno A, Kawamura T, Ogawa A, Takayasu H. Relation of spontaneous passage of ureteral calculi to size. Urol 1977;10(6):544–6.

[13] Porpiglia F, Destefanis P, Fiori C, Fontana D. Effectiveness of nifedipine and deflazacort in the management of distal ureter stones. Urol 2000;56(4):579–82.

[14] Hollingsworth JM, Rogers MA, Kaufman SR, Bradford TJ, Saint S, Wei JT, et al. Medical therapy to facilitate urinary stone passage: a meta-analysis. Lancet 2006;368(9542):1171–9.

[15] Lipkin M, Shah O. The use of alpha-blockers for the treatment of nephrolithiasis. Rev Urol 2006;8(Suppl. 4):S35–42.

[16] Mitra SK, Gopumadhavan S, Venkatarangannna MV, Sundaram R. Effect of cystone, a herbal formulation, on glycolic acid-induced urolithiasis in rats. Phytotherapy Res 1998;12:372–4.

[17] Jethi RK, Duggal B, Sahota RS, Gupta M, Sofat IB. Effect of the aqueous extract of an Ayurvedic compound preparation on mineralization & demineralization reactions. Indian J Med Res 1983;78:422–5.

[18] Nandini M, Sofat IB, Jethi RK. Effect of an ayurvedic compound preparation on the ability of rat urine to influence mineral phase formation. Indian J Med Res 1989;90:77–81.

[19] Mahadev R, Ravo MNA. Protective effects of Cystone, a polyherbal Ayurvedic preparation on cisplatin-induced renal toxicity in rats. J Ethnopharmacol 1998;62:1–6.

[20] Shrivastava JG. Herbal plants used in stone. Quart J Crude Drug Res 1971;11:1683–9.

[21] Joshi VS, Parekh BB, Joshi MJ, Vaidya AD. Inhibition of the growth of urinary calcium hydrogen phosphate dihydrate crystals with aqueous extracts of *Tribulus terrestris* and *Bergenia ligulata*. Urol Res 2005;33(2):80–6.

[22] Satish H, Umashankar DC. Comparative study of methanolic extract of *Bergenia ligulata yeo*., with isolated constituent bergenin in urolithiatic rats. Biomedicine 2006;1(1):80–6.

[23] Umashankar D, Chandra R, Chawla AS, Deepak M, Singh D, Handa SS. High pressure liquid chromatographic determination of bergenin and (+)-afzelechin from different parts of Paashaanbhed (Bergenia ligulata yeo). Phytochem Anal 1999;10(1):44–7.

[24] Kasture SB, Kasture VS, Chopde CT. Anti-inflammatory activity of *Rubia cordifolia* roots. J Nat Rem 2001;2:111–5.

[25] Divakar K, Pawar AT, Chandrasekhar SB, Dighe SB, Divakar G. Protective effect of the hydro-alcoholic extract of *Rubia cordifolia* roots against ethylene glycol induced urolithiasis in rats. Food Chem Toxicol 2010;48(4):1013–8.

[26] Gilani AH, Janbaz KH, Zaman M, Lateef A, Tariq SR, Ahmad HR. Hypotensive and spasmolytic activities of crude extract of *Cyperus scariosus*. Arch Pharmacol Res 1994;17(3):145–9.

[27] Mohamed Farook NA, Rajesh S, Jamuna M. Inhibition of mineralization of urinary stone forming minerals by medicinal plants. Eur J Chem 2009;6(3):938–42.

[28] Khare CP. Encyclopedia of Indian medicinal plants. Springer; 2007. pp. 337–338.

[29] Iwalewa EO, Iwalewa OJ, Adeboye JO. Analgesic, antipyretic, anti-inflammatory effects of methanol, chloroform and ether extracts of *Vernonia cinerea* less leaf. J Ethnopharmacol 2003;86(2–3):229–34.

[30] Gupta M, Mazumder UK, Manikandan L, Haldar PK, Bhattacharya S, Kandar CC. Antibacterial activity of *Vernonia cinerea*. Fitoterapia 2003;74(1–2):148–50.

[31] Sushruta. Treatment of Ashmari. In: Shastri KA, editor. Sushruta Samhita Chikitsasthanam. 4th ed. Varanasi: Chaukhambha Sanskrit Sansthan; 1976. p. 41.