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Effect of Cystone® on urinary composition and stone formation over a one year period☆

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ABSTRACT

Kidney stones are a common problem for which inadequate prevention exists. We recruited ten recurrent kidney stone formers with documented calcium oxalate stones into a two phased study to assess safety and effectiveness of Cystone®, an herbal treatment for prevention of kidney stones. The first phase was a randomized double-blinded 12 week cross over study assessing the effect of Cystone® vs. placebo on urinary supersaturation. The second phase was an open label one year study of Cystone® to determine if renal stone burden decreased, as assessed by quantitative and subjective assessment of CT. Results revealed no statistically significant effect of Cystone® on urinary composition short (6 weeks) or long (52 weeks) term. Average renal stone burden increased rather than decreased on Cystone®. Therefore, this study does not support the efficacy of Cystone® to treat calcium oxalate stone formers. Future studies will be needed to assess effects on stone passage, or on other stone types.

Introduction

Kidney stones are a global affliction causing a great deal of morbidity and economic loss (Saigal et al. 2005). The prevalence of nephrolithiasis increases as societies become industrialized (Goldfarb 2003; Stamatelou et al. 2003; Sowers et al. 1998). Therefore, the worldwide burden is likely to increase in future years. A method to prevent kidney stones would be an obvious benefit. Existing treatments with evidence that supports their long term efficacy to prevent calcium oxalate kidney stones include dietary and lifestyle changes, as well as chronic use of one of three medications (thiazides, potassium citrate, and allopurinol). No new treatments have been established in decades, and these that are available have inherent problems related to patient compliance, cost, effectiveness and side effects. Therefore, a preventive treatment that would be easy to take, low in cost, safe and effective would be highly desirable.

Cystone® tablets are an Ayurvedic treatment for stones, traditionally practiced in India. Many studies and long experience attest to the safety of this compound. It is also claimed that Cystone® decreases urinary supersaturation or micropulverizes and expels kidney stones, but existing studies have been limited by small patient numbers, weak methodology, and poor study design including lack of proper controls. Therefore, in this study we rigorously evaluated the ability of Cystone® to decrease urine supersaturation and to prevent new stone formation and growth of existing stones via a short-term randomized, placebo-controlled, double-blinded, cross over study (to evaluate effects on urinary chemistries), followed by an open label extension (to evaluate effects on stone burden) (Fig. 1). Quantitative computerized tomography (CT) was used to assess changes in stone burden over the time of the study.

Materials and methods

Study drug

Cystone® is traditionally used for relief of a variety of urological problems including nephrolithiasis and is comprised of the following substances: shilapuspha (Didymocarpus pedicellata) 130 mg, Pasanabheda (Saxifraga ligulata Syn. Bergenia ligulata/ciliata) 98 mg, Manjishtha (Rubia cordifolia) 32 mg, Nagarmusta (Cyperus scariosus) 32 mg, Apamarga (Achyranthes aspera) 32 mg, Gohija (Onosma bracteatum) 32 mg, Sahadevi (Vernonia cinerea) 32 mg, Shilajeet (Purified) 26 mg, and Hajrul yahood bhasma 32 mg. Its purported effect is to "prevent supersaturation of lithogenic substances, control oxamide (a substance that precipitates stone

Abbreviations: AU, Agatston Units; CT, computerized tomography; mm^3, cubic millimeter.

☆ Cystone® tablets and partial study funding were supplied by Himalaya Health Care.

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START	6 weeks		1 week	6 weeks		46 weeks	END
Urine supersaturation x 2 and Renal CT	Cystone	Urine supersaturation x 2	washout	Placebo	Urine Supersaturation x 2	Cystone	Urine supersaturation x 2 and Renal CT
	Placebo	Urine supersaturation x 2	washout	Cystone	Urine Supersaturation x 2	Cystone	

Fig. 1. Study flow chart.

formation) from the intestine and correct the crystalloid–colloid imbalance. Cystone® inhibits calculogenesis by reducing stone-forming substances like oxalic acid, calcium hydroxyproline, etc., and causes their expulsion by micropulverization. Cystone® causes disintegration of the calculi and crystals by acting on the mucin, which binds the particles together. Cystone®'s antimicrobial activity is beneficial in the prevention of urinary tract infections associated with urinary stones and crystalluria. Cystone®'s antispasmodic and anti-inflammatory activities relieve ureteric colic and alleviate symptoms of painful and burning and micturition." (http://himalayahealthcare.com/products/cystone.htm). Cystone® is manufactured and sold virtually world wide by Himalaya Health Care. In the United States, the product is known as Uricare®.

Study subjects

Ten patients (4 men, 6 women) with recurrent, analytically confirmed, calcium-containing kidney stones were recruited from the Mayo Stone Clinic. All were Caucasian adults and had passed at least one stone at entry into the study (Table 1). Metabolic activity prior to study entry was defined as an increase in stone size or number documented on a previous CT scan obtained within one year prior to study entry. Only two patients were metabolically active at entry into the study. Exclusions included age under 18 years, pregnancy, refusal to use an effective method of birth control during the study, chronic urinary infection, secondary causes of kidney stones, (e.g., bowel disease, renal tubular acidosis, primary hyperoxaluria) or mental incompetence to give informed written consent on a form approved by the institutional review board. All patients were allowed to continue their existing kidney stone treatment programs. All patients promptly began the study after consenting to be enrolled.

Study design and conduct

The protocol is illustrated in Fig. 1. Patients were randomly assigned by Mayo Clinic Research Pharmacy to a 6 week treatment program with Cystone® tablets, 2 by mouth twice daily, or identical placebo. This is the dose recommended by the manufacturer. After a 1 week washout the patients crossed over to the alternate treatment for another 6 weeks. Patients provided two 24-h urine collections shortly before starting the study, at the end of the first 6 weeks of treatment, and again at the end of the 6 week cross over, each of which were analyzed for determinants of urinary supersaturation in the Mayo Renal Function Laboratory and calculated using the Equil2 program (Werness et al. 1985). After completing both crossover arms, patients then immediately took Cystone® open label in the same dose for an additional 48 weeks, thus ensuring a 52 week total exposure to Cystone® during the 59 week study. Quantitative noncontrast multidetector CT exams were all performed on a 64-channel MDCT scanner (Sensation-64, Siemens Medical Solutions, Forschheim, Germany). For the 64-channel technique, patients were in the supine position on the CT table with arms above the head. An initial survey topogram was obtained for positioning purposes (80 kVp, 300 mA) from the top of the liver through the pubic symphysis. Subsequent CT images were obtained in a single breath-hold through the kidneys. A standardized acquisition protocol was used for all exams (collimation 64×0.6; gantry rotation time, 0.5 s; table feed, 23 mm/rotation (pitch of 1.2); quality reference 240 mA s; 120 kVp and the field of view was adjusted to patient size). Three reconstruction intervals were obtained from the raw data including: 5.0 mm thickness at 5.0 mm intervals (axial), 2.0 mm thickness at 2.0 mm intervals (axial) and 2.0 mm thickness at 2.0 intervals (coronal adjusted to the long axis of the kidneys). The 2.0 mm thickness at 2.0 mm interval (axial) data set was also processed at a free standing 3D workstation (Vitrea, Vital Images, Inc., Minnetonka, MN) by dedicated 3D technologists to obtain quantitative calcium scoring data for each kidney. All scored images were reviewed to determine that the included calcifications were consistent with urolithiasis rather than renal arterial or parenchymal calcifications. The scoring programs are typically used for coronary artery calcification quantification and generate both an Agatston score (reported as Agatston Units, AU) and volumetric score (reported as mm^3). In the algorithms positive calcification required a minimum density threshold of 130 Hounsfield Units and a minimum area threshold of 3 adjacent pixels of at least 130 Hounsfield Units. In addition to quantified scoring, all images including the axial and reconstructed coronal series were reviewed by the diagnostic radiology service and a clinical report was generated. These images were subsequently sent to a picture archiving and communication system and available for referring clinicians. In addition, all images were reviewed by a radiologist (TJV) in a blinded fashion to score each kidney as increased, no change, or decreased stone burden.

Statistics and randomization

Randomization was accomplished using a table provided by the department of statistics to the study coordinator who was blinded as to whether the patients received placebo or Cystone®. Biochemical and supersaturation results were analyzed via a matched pair analysis using the JMP software package (SAS Instituted, Inc.); P values <0.05 were deemed significant.

Results

Table 1 contains demographic and clinical characteristics of the study patients. Patients who consented to participate in the Cystone® study tended to have recurrent kidney stones inadequately controlled on their current program. This tended to select a more difficult-to-treat patient population. One patient thought that Cystone® could be discriminated from placebo by its "peppery" taste. The other study participants did not identify this difference.

Table 2 displays the 24 h urinary supersaturation results. In a matched pair analysis of the initial crossover study no statistically significant differences for any parameter between Cystone® treatment as compared to placebo were present. Similarly, the 24-h urine chemistries did not differ after one year on Cystone®, as compared to values on placebo during the initial crossover period. Therefore, there was no evidence that Cystone® altered urinary chemistries after short term (6 weeks) or long term (1 year) usage.

Table 3 contains results of CT studies at baseline and one year. The blinded radiologist's opinion of changes in kidney stone burden

Table 1
Patient characteristics.

PT	Age	Race	Gender	Stone composition	Placebo detection	Metabolic activity	Risk factors	Relevant medications
1	36	W	F	CaOx 60–70% CaP 30–40%	No	Active	MSK 1+ Ca	Self decreased Cystone® to 1 b.i.d.
2	71	W	M	CaOx 100%	No	Active	HTN	HCT 25 mg/day
3	47	W	F	CaOx 100%	No	Indeterminate	FH Obesity	None
4	53	W	M	CaOx 100%	No	Active	HCa	None
5	57	W	M	CaOx	No	Indeterminate	FH HC Obese	None
6	47	W	F	CaOx 10–20% CaP 80–90%	Yes	Active	HCa HCP Osteoporosis	HCT 25 mg/day Calcium 1600 mg/day Fosamax 70 mg/week
7	44	W	F	CaOx 70–100% CaP 80–90%	No	Inactive	FH	Ammonium chloride 500 mg q.i.d.
8	75	W	M	CaOx	No	Inactive	HC HO	None
9	50	W	F	CaOx 40–90% CaP 60–100%	No	Indeterminate	FH, HTN Obese, HCa	None
10	45	W	F	Calcium	No	Indeterminate	LV, HC	None

W – white, F – female, M – male, CaOx – calcium oxalate, CaP – calcium phosphate, MSK – medullary sponge kidney, HCa – hypercalciuria, HCi – hypocitraturia, HTN – hypertension, FH – family history, LV – low urine volume, HO – hyperoxaluria.

Table 2
Urine supersaturation.

PT	Start			After placebo (6 weeks)			After Cystone® (6 weeks)			End Cystone® (≥48 weeks)		
	CaOx	Br	HAP	CaOx	Br	HAP	CaOx	Br	HAP	CaOx	Br	HAP
1	1.50	1.84	5.59	2.14*	1.59*	5.86*	1.85*	1.63*	4.78*	2.41*	1.49*	5.21*
2	1.61	1.19	4.21	0.90	−0.81	3.03	0.93	−1.39	2.41	1.15	−2.82	−0.45
3	1.92	−0.78	3.12	1.99	0.43	4.64	2.20	0.36	4.01	1.84	0.08	3.95
4	1.97	−0.57	2.83	2.37	0.58	5.15	2.36	0.14	4.50	1.97	−0.09	4.31
5	2.05	−1.45	0.69	1.75	1.59	5.40	1.99	0.16	3.80			
6	1.98	1.23	5.90	1.43	0.73	6.69	2.21	1.75	8.01	2.22	1.46	7.25
7	1.90	0.69	6.04	2.19	1.18	5.79	1.71*	1.05*	7.31*	1.13	−1.12	5.05
8	2.24	0.98	7.59	1.90	−0.49	2.90	2.04	−0.03	4.11	2.17	−0.25	4.23
9	1.45	−0.14	3.09	1.79	1.25	5.13	1.59	0.05	2.95	1.78	0.06	3.00
10	2.08	0.55	3.44	1.92	1.25	5.61				1.38	0.96	4.25

CaOx – calcium oxalate, Br – calcium phosphate (brushite), HAP – calcium phosphate (hydroxyapatite).

Table 3
CT scores.

Patient	Baseline volume	Baseline Agatston	One year volume	One year Agatston	Radiologist impression	Clinical events
Right kidneys						
1	10	6	9	6	NC	None
2	47	50	58	70	I	None
3	0	0	5	2	NC	None
5	ND	ND	132	110	NC	None
6	29	35	4	1	D	PSD ST
7	59	58	73	72	NC	None
8	159	184	196	217	I	None
9	60	65	77	81	NC	PSD ST?
10	0	0	0	0	NC	None
Mean	45.5	49.75	52.75	56.125		
SD	52.03021	60.24415	66.43955	74.23407		
P vs. baseline			0.811732	0.853223		
Left kidneys						
1	12	8	27	24	I	None
2	2	1	0	0	NC	None
3	5	4	4	3	D	None
5	ND	ND	285	352	I	None
6	582	709	790	1053	I	None
7	205	257	233	264	I	PSD ST
8	121	127	143	161	I	None
9	203	223	194	229	NC	PSD ST?
10	0	0	3	1	I	PSD ST
Mean	141.25	166.125	174.25	247.7143		
SD	198.9829	243.1604	265.7398	371.4645		
P vs. baseline			0.783027	0.630765		

I – increased stones, D – decreased stones, NC – no change in stones, ND – not done, PSD ST – passed stone.

generally agreed with the quantitative data, with the exception of both kidneys in patient 4. We have no explanation for this discrepancy. Patient 4 was excluded from CT analysis because of bilateral stone removal surgery during the study. Therefore, we evaluated 18 of 20 kidneys for stone burden. Spontaneous stone passage occurred from 4 of 18 kidneys during the study. Nevertheless, the official radiology interpretation was that 8 kidneys had increased stone material, 8 kidneys were unchanged, and only 2 kidneys had decreased stone material. Quantitative scoring of renal calcium content in 18 kidneys from these same 9 patients revealed that mean total stone burden per kidney increased over this time period as assessed by the volumetric scoring system (93–114 mm^3; $P = 0.07$ by matched pairs analysis) or the Agatston scoring system (108–136 AU; $P = 0.10$ by matched pairs analysis). These results did not support an overall positive effect off Cystone® on stone burden.

No patients described any side effects attributable to Cystone®, consistent with previous studies.

Discussion

Current non-surgical therapies of kidney stones take 3 different approaches. Prevention, either primary or secondary is preferred. Indeed, evidence exists that supports the prescription of specific dietary measures and/or drugs for this purpose. Chemolysis (dissolution) of existing stones may be possible with uric acid and some cystine stones. No scientific data supports the feasibility of calcium stone chemolysis, to our knowledge. Expulsion therapy to help pass stones that have moved into the ureter (but not stones resident in the kidney) is, however, supported by recent controlled trials (Hollingsworth et al. 2006).

Randomized controlled studies exist to support the efficacy of thiazides (Ettinger et al. 1988), allopurinol (Ettinger et al. 1986), and potassium magnesium citrate (Ettinger et al. 1997) for secondary prevention of calcium oxalate kidney stones. Side effects, cost, and imperfect prevention make the ready availability of cheap, safe and effective stone prevention therapy highly desirable.

Current treatments for stone prevention typically decrease urinary supersaturation by affecting urinary composition (e.g., decrease calcium excretion). No agent is known that can be safely taken and enter the urine to decrease calcium oxalate crystallization, or perhaps even better dissolve calcium oxalate stones and/or crystals. If such a compound were found, it would represent a new class of treatment for renal stones. Several herbs have been purported to decrease stone risk, or hasten stone passage. However, hard scientific evidence regarding their efficacy is scanty. The Chinese Kampou medicine has been used to treat disease for centuries, including for prevention and treatment of urinary calculi. An experimental study suggested an inhibitory effect of Kampou extracts on *in vitro* CaOx crystallization (Koide et al. 1995). In this report, the two species from Kampou (Takusya and Kagosou) also were effective for preventing renal crystallization in a rat nephrolithiasis model; similar results were obtained in a second report (Yasui et al. 1999). Chorey-to, another Chinese medicine which contains Takusya, also exhibited a protective effect in rats rendered hyperoxaluric with ethylene glycol, even though urinary citrate levels fell (Calixto et al. 1998).

Many stone patients in Brazil take a tea made from the annual herb *Phyllanthus niruri* that grows in the tropical indigenous area and does not cause side effects (Calixto et al. 1998). This natural product has been called “break stone” because it has been used for generations to eliminate gallstones and kidney stones (Calixto et al. 1998). Diverse classes of potentially active compounds have been identified from genus *Phyllanthus*, including alkaloids, flavonoids, lactones, steroids, terpenoids, lignans, and tannins. Some researchers have demonstrated antispasmodic and analgesic activities in *Phyllanthus niruri* which could explain the popular use of the plant for kidney and bladder stones (Calixto et al. 1998; Santos et al. 1994) The alkaloid extract caused smooth muscle relaxation specific to the urinary and biliary tract which could facilitate the expulsion of both kind of stones (Calixto et al. 1984). *Phyllanthus niruri* has also been shown to inhibit CaOx endocytosis by renal tubular cells (Campos and Schor 1999), another mechanism by which this agent could decrease crystal retention in the kidney, and in a small clinical trial appeared to reduce urinary calcium excretion amongst hypercalciuric stone formers (Nishiura et al. 2004). No toxicity was apparent in the latter study. A Moroccan herb *Herniaria hirsuta* has similarly been evaluated for effects on CaOx crystallization, including by our group (Atmani et al. 2004). Interestingly, *Phyllanthus niruri* is purported to act by promoting nucleation of more crystals that achieve a smaller size.

A major shortcoming of prevention trials to date is the lack of adequate end points. Typically, the hard end point in most trials is stone passage rate, even though there has not been any data to suggest that any current treatment prevents passage of preformed stones. This formulation presumes relatively tight correlation between stone burden and stone passage rates. Although it is true that one cannot pass a stone unless it has developed and grown, the time between stone development and passage appears to be variable and unpredictable. Therefore, the ability to accurately measure stone size *in vivo* over time could represent a valuable surrogate end point for clinical trials in the future. Stone risk, composition, and risk of recurrence all correlate with urinary supersaturation, as calculated using the iterative computer program Equil2 (Parks et al. 1997). Therefore, urinary supersaturation is a second potential surrogate endpoint for clinical trials. In this study we assessed the effect of Cystone®, a common stone prevention treatment outside of Europe and the United States, on both urinary supersaturation and radiographically assessed stone burden.

The current results did not document any beneficial effect of Cystone® on the urinary composition. However, the failure to find statistically significant change in urinary supersaturation does not rule out a beneficial effect. Equil2 only calculates SS based upon the inorganic composition of urine (Werness et al. 1985), and does not take into account the potential effect of potential macromolecular inhibitors such as Tamm–Horsfall protein or osteopontin (Kumar et al. 2005), or smaller molecules such as phytate (Grases et al. 2000). Furthermore, Cystone® could exert effects on other ion pairs that can form in urine and influence growth of calcium oxalate crystals, but are not included in the Equil2 calculations (Rodgers et al. 2006).

Cystone® is purported to promote stone passage. However, on average stone burden increased rather than decreased in our study. It is important to note that stone formers in this study tended to be those who had failed standard therapy, which may have influenced the end point of stone formation and passage. It is also possible an effect may have been apparent with longer follow up.

No patient reported any side effects from Cystone®. This is in accord with previously published studies.

Conclusion

This short term study does not suggest that Cystone® affects those urinary chemistries commonly measured and known to influence calcium oxalate stone formation, nor does decrease renal calcium stone burden over a 1 year period. It is possible elements of the urine were affected that are not typically measured (e.g., glycoprotein inhibitors). A longer term study with more patients would be necessary to detect changes in stone events or enhanced stone

passage, or effects on other stone types. In any new study of Cystone, the botanical authenticity of each individual herb will need to be documented by the manufacturer using high pressure liquid chromatography. This short term trial failed to find evidence that Cystone® prevents kidney stone formation and growth in recurrent calcium oxalate stone formers.

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References

Atmani, F., Slimani, Y., Mimouni, M., Aziz, M., Hacht, B., Ziyyat, A., 2004. Effect of aqueous extract from Herniaria hirsuta L. on experimentally nephrolithiasic rats. J. Ethnopharmacol. 95, 87–93.

Calixto, J.B., Santos, A.R., Cechinel Filho, V., Yunes, R.A., 1998. A review of the plants of the genus Phyllanthus: their chemistry, pharmacology, and therapeutic potential. Med. Res. Rev. 18, 225–258.

Calixto, J.B., Yunes, R.A., Neto, A.S., Valle, R.M., Rae, G.A., 1984. Antispasmodic effects of an alkaloid extracted from Phyllanthus sellowianus: a comparative study with papaverine. Braz. J. Med. Biol. Res. 17, 313–321.

Campos, A.H., Schor, N., 1999. Phyllanthus niruri inhibits calcium oxalate endocytosis by renal tubular cells: its role in urolithiasis. Nephron 81, 393–397.

Ettinger, B., Citron, J.T., Livermore, B., Dolman, L.I., 1988. Chlorthalidone reduces calcium oxalate calculous recurrence but magnesium hydroxide does not. J. Urol. 139, 679–684.

Ettinger, B., Pak, C.Y., Citron, J.T., Thomas, C., Adams-Huet, B., Vangessel, A., 1997. Potassium-magnesium citrate is an effective prophylaxis against recurrent calcium oxalate nephrolithiasis. J. Urol. 158, 2069–2073.

Ettinger, B., Tang, A., Citron, J.T., Livermore, B., Williams, T., 1986. Randomized trial of allopurinol in the prevention of calcium oxalate calculi. N. Engl. J. Med. 315, 1386–1389.

Goldfarb, D.S., 2003. Increasing prevalence of kidney stones in the United States. Kidney Int. 63, 1951–1952.

Grases, F., March, J.G., Prieto, R.M., Simonet, B.M., Costa-Bauza, A., Garcia-Raja, A., Conte, A., 2000. Urinary phytate in calcium oxalate stone formers and healthy people. Scand. J. Urol. Nephrol. 34, 162–164.

Hollingsworth, J.M., Rogers, M.A.M., Kaufman, S.R., Bradford, T.J., Saint, S., Wei, J.T., Hollenbeck, B.K., 2006. Medical therapy to facilitate urinary stone passage: a meta-analysis. Lancet 368, 1171–1179.

Koide, T., Yamaguchi, S., Utsunomiya, M., Yoshioka, T., Sugiyama, K., 1995. The inhibitory effect of Kampou extracts on in vitro calcium oxalate crystallization and in vivo stone formation in an animal model. Int. J. Urol. 2, 81–86.

Kumar, V., Pena de la Vega, L., Farell, G., Lieske, J.C., 2005. Urinary macromolecular inhibition of crystal adhesion to renal epithelial cells is impaired in male stone formers. Kidney Int. 68, 1784–1792.

Nishiura, J.L., Campos, A.H., Boim, M.A., Heilberg, I.P., Schor, N., 2004. Phyllanthus niruri normalizes elevated urinary calcium levels in calcium stone forming (CSF) patients. Urol. Res. 32, 362–366.

Parks, J.H., Coward, M., Coe, F.L., 1997. Correspondence between stone composition and urine supersaturation in nephrolithiasis. Kidney Int. 51, 894–900.

Rodgers, A., Allie-Hamdulay, S., Jackson, G., 2006. Therapeutic action of citrate in urolithiasis explained by chemical speciation: increase in pH is the determinant factor. Nephrol. Dial. Transplant. 21, 361–369.

Saigal, C.S., Joyce, G., Timilsina, A.R., 2005. Direct and indirect costs of nephrolithiasis in an employed population: opportunity for disease management? Kidney Int. 68, 1808–1814.

Santos, A.R., Filho, V.C., Niero, R., Viana, A.M., Moreno, F.N., Campos, M.M., Yunes, R.A., Calixto, J.B., 1994. Analgesic effects of callus culture extracts from selected species of Phyllanthus in mice. J. Pharm. Pharmacol. 46, 755–759.

Sowers, M.R., Jannausch, M., Wood, C., Pope, S.K., Lachance, L.L., Peterson, B., 1998. Prevalence of renal stones in a population-based study with dietary calcium, oxalate, and medication exposures. Am. J. Epidemiol. 147, 914–920.

Stamatelou, K.K., Francis, M.E., Jones, C.A., Nyberg, L.M., Curhan, G.C., 2003. Time trends in reported prevalence of kidney stones in the United States: 1976–1994. Kidney Int. 63, 1817–1823.

Werness, P.J., Brown, C.M., Smith, L.H., Finlayson, B., 1985. EQUIL2: a BASIC computer program for the calculation of urinary saturation. J. Urol. 134, 1242–1244.

Yasui, T., Fujita, K., Sato, M., Sugimoto, M., Iguchi, M., Nomura, S., Kohri, K., 1999. The effect of Takusya, a Kampou medicine, on renal stone formation and osteopontin expression in rat urolithiasis model. Urol. Res. 27, 194–199.