ORIGINAL ARTICLE

Safety and efficacy of a polyherbal formulation from traditional Persian medicine in patients with calcium kidney stones: A randomized, double-blinded clinical trial

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Background: 10%–15% of the world's population suffers from kidney stones. Nearly 50% increase was observed in diagnosing and treating nephrolithiasis in the last decades. Effective medical treatment for the disease is not yet well established. Moreover, there is an increasing global demand to manage diseases using complementary and alternative medicine. This study aimed to formulate and assess the safety and efficacy of a multi-ingredient formulation from traditional Persian medicine (TPM) known as *Mofatet* powder in patients suffering from calcium kidney stones. **Materials and Methods:** The aqueous extract of *Mofatet* powder was prepared, freeze-dried, and formulated as capsules. 26 patients in the drug group and 25 patients in the placebo group used 500 mg capsules of the drug/placebo twice daily for 5 weeks. Ultrasonography/kidney, ureter and bladder imaging, urine analysis, and biochemical parameters were evaluated before and after the intervention. **Results:** The imaging results showed a 60.73% decrease ($P < 0.001$) in stone size in the drug group. Moreover, the urinary calcium decreased ($P = 0.02$) and the urinary magnesium increased ($P < 0.001$) in the drug group. No remarkable changes were observed in the placebo group in these parameters. No significant effect was observed in aspartate transaminase, alanine transaminase, serum creatinine, and blood urea nitrogen levels in none of the groups. **Conclusion:** This study suggests that *Mofatet* powder was effective in reducing calcium kidney stones size with no potential nephro/hepatotoxicity. After confirming these results in larger clinical trials with longer duration, this formulation can be considered a treatment for nephrolithiasis.

Key words: Calcium oxalate, clinical trial, kidney calculi, Persian traditional medicine, polyherbal formulation

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INTRODUCTION

10%–15% of the world's population suffers from nephrolithiasis during their lifespan. On average, 6% of women and 12% of men deal with kidney stones, mainly within 20–49 years of age.[1,2] Nearly 50% increase was observed in diagnosing and treating nephrolithiasis in the last decades.

The economic burden of disease is estimated to be 2.1–5.3 billion US$ in the USA annually.[3] It has a recurrence rate of 70%–80% in males and 47%–60% in females. The highest recurrence rate is observed with calcium stones.[4]

Among calcium stones, 50% are pure calcium oxalate, 5% are calcium phosphate, and 45% are a mixture of both.[5] Supersaturation of ions leads to crystallization.

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The crystal's growth forms large lumps or leads to stone formation.[6]

Hyperuricosuria, hypercalciuria, hyperoxaluria, hypocitraturia, hypomagnesuria, hypercystinuria, and urinary pH of 5.0–6.5 promote calcium oxalate stone formation.[7]

Nausea, vomiting, fever, chills, renal colic, flank pain, discomfort/pain during urination, and hematuria are signs and symptoms associated with nephrolithiasis. Moreover, kidney stones may increase the risk of chronic kidney diseases (CKD),[8] diabetes, and cardiovascular diseases.[6]

Besides nonpharmacological therapies such as lowering sodium, oxalate, and animal protein intake, pharmacologic treatment should be considered. Common medicines include thiazide diuretics for hypercalciuria management, potassium citrate to reduce hypocitraturia, and regulation of urinary tract pH. Allopurinol is also used to control hyperuricemia and hyperuricosuria.[9]

Extracorporeal shock wave lithotripsy, percutaneous nephrolithotomy, ureteroscopy, laser therapy, and surgery are other ways to manage kidney stones. Disadvantages of the current medicaments include high costs, invasiveness, side effects, and disability to alleviate the sharp pain associated with kidney stones.[10]

As mentioned, effective medical treatment for the disease is not yet well established.[11] Moreover, there is an increasing global demand to manage various diseases with natural medicine and medicaments originating from complementary and alternative medicine.[12] Traditional Persian medicine (TPM) is an old medical system with knowledge derived from Chinese, Indian, and traditional Egyptian medicine.[13]

Many medications for kidney/bladder stones have been reported in TPM pharmaceutical manuscripts. In reviewing TPM pharmacopeias,[14-17] we found a polyherbal formulation known as *Mofatet powder* containing equal parts of *Cucumis sativus* L. (seed), *Cucurbita pepo* L. (seed), *Apium graveolens* L. (seed), *Foeniculum vulgare* Mill (seed), *Pimpinella anisum* L. (seed), and *Tribulus terrestris* L. (fruit). Based on TPM pharmacopeias, it has been reported to consume 5 g of the mixture powder twice daily (once in the morning on an empty stomach, and once at night before sleeping). Equal parts of ingredients should be prepared, boiled for 10 min, and consumed orally. To facilitate consumption and increase patient compliance, uniformity of preparation, and stability of the aqueous extract obtained from this powder, we aimed to reformulate it as capsules by freeze-drying the aqueous extract. The present study aimed to evaluate this formulation's efficacy in terms of reduction in stone size and safety in terms of nephro/hepatotoxicity as well as possible involved mechanisms, in a randomized and double-blinded clinical trial.

MATERIALS AND METHODS

Formulation preparation

Preparation of formulation components

Formulation components were purchased from a local market in Shiraz, Iran. A paleontologist identified components at the Department of Paleontology, Shiraz University, and a voucher specimen from each plant was deposited in the Shiraz School of Pharmacy collection.

Preparation of aqueous extract

1.2 kg of each component was prepared and mixed with an electric grinder. To increase the particle size hemogenicity, the powder was passed through a sieve with a mesh number of 30. Then, each 500 g of the powder mixture containing equal part of ingredients was boiled in 5 L of distilled water for 10 min to obtain an aqueous extract. Then, the obtained aqueous extract was filtered using the vacuum pump, the solid component was separated, and the aqueous extract was used for the next steps.

Concentrating the aqueous extract

The aqueous extract of the powder was concentrated using a rotary evaporator (Heidolph, Germany). Nearly 40% (8 L of a 20-L balloon) of the capacity of a rotary evaporator was filled with the aqueous extract each time. By adjusting the temperature (55°C) and applying a vacuum, the distillation process of the aqueous extract was performed, and the concentrated extract was obtained. This process took about 4 h each time.

Freeze-drying process

The freeze-drying process was done using a freeze dryer (Zirbush, Germany). About 1 L of concentrated aqueous extract was filled into a 2-L balloon for freeze-drying. First, the concentrated extract was frozen at –60°C for 24 h. Then, the sublimation of the aqueous solvent was completed using the freeze-dryer, and the resulting powder was collected.

Capsule filling

In this study, capsules were prepared from the concentrated aqueous extract of the powder after being freeze-dried in an amount equivalent to the traditional dosage. Placebo was also prepared from roasted starch with 10% of the mixture of plants present in the formulation. Then, the powder obtained from the freeze-drying process and placebo were passed through a sieve with mesh numbers 30 and 500 mg filled in each zero-size capsule. Weight variation was evaluated using the United States Pharmacopeia (USP) protocol for content uniformity.

Study design

A double-blind, randomized placebo-controlled clinical trial was performed to evaluate the safety and efficacy of *Mofatet* powder in patients suffering from calcium stones. Participants were recruited from February 2020 to March 2021 in the Shahid Motahari and Emam Reza Clinic of the Shiraz University of Medical Sciences. Kidney stone diagnosis was confirmed using kidney, ureter, and bladder (KUB), ultrasonography, or a noncontrast spiral computed tomography scan. Composition analysis was used to determine the stone type. Patients older than 18 years with renal stones 5 mm or bigger in the lower pole of the kidney were included in the study. Patients with severe urinary tract infection, acute kidney injury, CKD, diabetes, ulcer disease, concurrent use of herbal medicines for dissolving kidney stones such as Sankol®, Rowatinex®, Cystone®, Lithorex-B® or Urtica ZardBand®, and pregnant or lactating women were excluded from the study. A computer-generated statistical program determines the sample size and randomization. By considering $\alpha = 0.05$, $\beta = 0.1$, and a power of 90%, the minimum sample size for each group was 13 patients based on a previous study and consultation with a statistician.[18] A total number of 51 patients were randomized into two groups (25 patients in the placebo group, and 26 patients in the drug group). The block randomization method (block number: 4) was used to randomize the patients. To conceal the allocation, sequentially numbered, opaque, sealed envelopes were used. Each envelope was labeled with a serial number and was handed to a third person (the secretary of the clinic) who opened the sealed envelope once a patient had consented to participate and assigned a treatment group. The drug group received two capsules of the drug daily (one in the morning on an empty stomach, and one at night before sleeping) for 5 weeks. The placebo group received identical-looking placebo capsules in the same order. All patients were allowed to use painkillers if required. No dietary restrictions were considered for patients. All patients were clinically examined at the beginning and after 5 weeks. KUB/ultrasonography imaging, urine analysis, and hematological and biochemical parameters were evaluated at the entry and after 5 weeks of treatment.

Outcome measures

Change in calculi size was considered the primary outcome measure. Secondary outcome parameters included changes in participants' plasma calcium, urine specific gravity, 24-h urine calcium, magnesium concentrations, and urine specific gravity. In terms of safety, the possible nephro/hepatotoxicity potential of the formulation was evaluated by considering changes in plasma concentrations of blood urea nitrogen (BUN), creatinine, alanine transaminase (ALT), and aspartate transaminase (AST).

Ethical issues

All patients filled out the informed consent form before entering the study. The trial was conducted based on the guidelines of the Declaration of Helsinki and reported using the recommendations for reporting randomized clinical trials as defined in the statement of Consolidated Standards of Reporting Randomized Clinical Trials.[19] The Ethics Committee of Shiraz University of Medical Sciences approved the study (Registration number: IR.SUMS.REC.1398.924). Moreover, the trial protocol was registered in the IRCT clinical trials database under the registration number: IRCT20191212045709N1.

Statistical analyses

IBM SPSS Statistics Version 20 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. The continuous data are expressed as mean ± standard deviation. The significance value was set at $P < 0.05$. The independent *t*-test was used for pretreatment comparison between groups. Due to the violation of normality based on the Shapiro–Wilk test, differences (post–pre) in the data between the two treatment groups were evaluated using the nonparametric Mann–Whitney test. The within-group differences were evaluated using the Wilcoxon signed-rank test.

RESULTS

From each 500 g primary mixture powder, 50 g dry powder was obtained after freeze-drying. As mentioned, the traditional dosing of the *Mofatet* powder is 5 g twice daily. Hence, 500 mg of freeze-dried powder twice daily would be equivalent to the traditional dosing. The mean weight of the 20 capsules was 0.496 g for drug capsules and 0.491 g for placebo capsules.

Out of 70 surveyed patients, 51 patients met the inclusion criteria and were randomized into two groups (25 patients in the placebo group, and 26 patients in the drug group). Two patients in the placebo group discontinued the treatment. Finally, 26 patients in the drug group and 23 patients in the placebo group completed the study [Figure 1].

The drug group consisted of 16 men and 10 women, and the placebo group consisted of 15 men and 8 women. The mean age for patients in the drug group was 51.41 ± 8.77 years, and the mean age for patients in the placebo group was 49.38 ± 9.41 years. There was no significant difference between the study groups in terms of age ($P = 0.903$). The average initial stone size was 8.15 ± 1.64 mm in the drug group and 7.95 ± 2.12 mm in the placebo group. There was no significant difference between the study groups in terms of stone size ($P = 0.361$). Other parameters, including BUN, creatinine, the volume of 24 h urine, urine specific gravity, urine calcium and magnesium, AST, ALT, and serum

calcium had no significant differences between the drug and placebo groups before treatment [Table 1].

The study showed a significant reduction in the calculi size after the treatment in the drug group ($P < 0.001$), while no remarkable difference was observed in the placebo group ($P = 0.39$).

The mean and percentage of change in stone size in the drug group were 3 mm and 60.73%, respectively. The difference in stone size change between the drug and placebo groups was also statistically remarkable ($P < 0.001$). The disappearance of stones was observed in two patients in the drug group. No disappearance of stones was observed in the placebo group. We found an increase in blood calcium levels of patients in the drug group compared with the same group before treatment ($P < 0.001$) and the placebo group after treatment ($P < 0.001$). There were no significant differences in the blood calcium levels of patients in the placebo group before and after treatment ($P = 0.6$).

After 5 weeks of treatment, urine calcium concentration decreased significantly in the drug group ($P = 0.02$). No significant differences in urine calcium concentrations were observed in the placebo group before and after the treatment ($P = 0.44$).

Urinary magnesium was increased in the drug group after 5 weeks of treatment compared with the same group before treatment and the placebo group after treatment ($P < 0.001$). No significant change was seen in the placebo group before and after treatment ($P = 0.72$).

Results showed no significant difference in urine volumes in the drug ($P = 0.32$) and placebo groups ($P = 0.42$) after 5 weeks of treatment.

The specific gravity of urine (as a promoter factor in nephrolithiasis) collected in 24 h after 5 weeks of treatment from patients in the drug group was less than the placebo group ($P = 0.015$). There were no significant differences in either group before and after the treatment.

Renal and hepatic function tests were done to access the probable nephro/hepatotoxicity potential of the formulation. There were no significant changes in BUN concentration before and after treatment ($P = 0.83$) in the drug group, or the placebo group ($P = 0.85$), or between the groups before and after treatment ($P = 0.92$). No significant

Table 1: Demographic data of patients before the entrance to the study

Parameter	Drug group (day=0)	Placebo group (day=0)	*P*
Age (years)	51.41±8.77	49.38±9.41	0.903
Stone size (mm)	8.15±1.64	7.95±2.12	0.361
BUN (mg/dL)	18.23±5.07	18.31±4.02	0.925
Serum creatinine (mg/dL)	1.07±0.25	1.11±0.26	0.717
Serum calcium (mg/dL)	9.13±0.22	9.07±0.23	0.662
AST (IU/L)	20.62±3.31	21.69±3.35	0.767
ALT (IU/L)	20.91±3.34	22.15±2.72	0.328
Urine specific gravity (g/mL)	1.07±0.42	1.05±0.62	0.558
24-h urine volume (L)	1.72±0.23	1.81±0.13	0.116
24-h urine calcium (mg)	163.33±12.49	158.69±18.22	0.152
24-h urine magnesium (mg)	2.86±0.33	2.94±0.38	0.989

BUN=Blood urea nitrogen; AST=Aspartate transaminase; ALT=Alanine transaminase

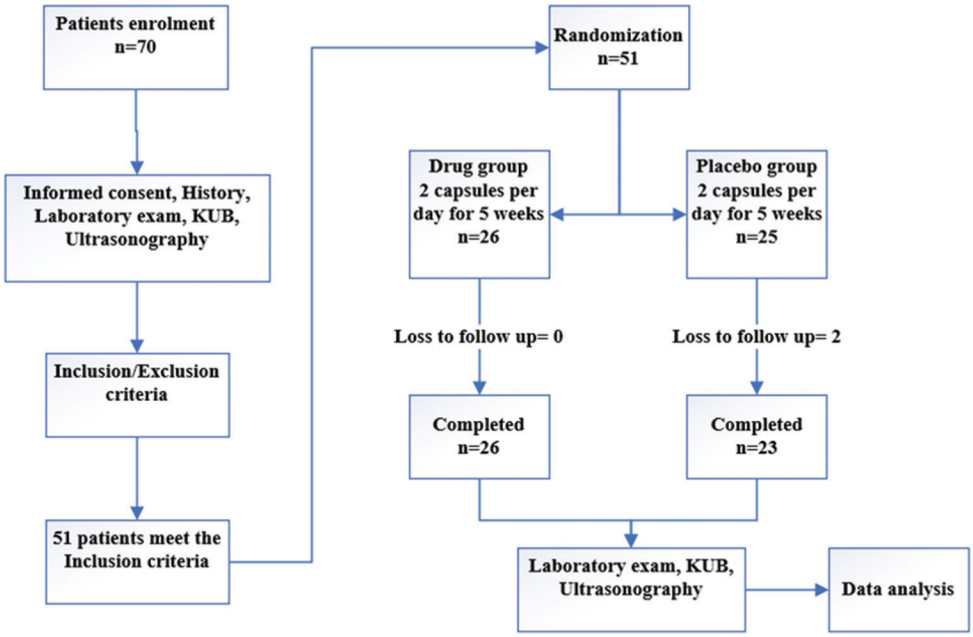

Figure 1: The Consolidated Standards of Reporting Randomized Clinical Trials diagram of the study. KUB = Kidney, ureter, and bladder

changes in serum creatinine concentration were found before and after treatment in the drug group ($P = 0.54$), the placebo group ($P = 0.37$), or between the groups after the treatment ($P = 0.48$). No significant changes in ALT or AST concentrations were found in the drug group ($P = 0.77$ and $P = 0.88$, respectively) and in the placebo group ($P = 0.84$ and $P = 0.44$, respectively) before and after treatment. Moreover, no significant changes were observed after treatment between groups ($P = 0.52$ and $P = 0.92$, respectively). No clinically significant adverse reactions were observed during the study [Table 2].

Table 2: Comparison of outcome measures after 5 weeks of treatment

Parameter	Drug group (day=0)	Drug group (after 5 weeks)	Percentage change	Drug group before and after treatment (*P*)	Placebo group (day=0)	Placebo group (after 5 weeks)	Percentage change	Placebo group before and after treatment (*P*)	The mean difference between groups after treatment (*P*)
Stone size (mm)	8.15±1.64	3.2±1.14	−60.73	<0.001	7.95±2.12	8.15±2.33	2.52	0.39	<0.001
BUN (mg/dL)	18.23±5.07	18.51±4.33	1.54	0.83	18.31±4.02	18.54±3.36	1.26	0.85	0.92
Serum creatinine (mg/dL)	1.07±0.25	0.96±0.22	−10.28	0.54	1.11±0.26	1.02±0.25	−8.11	0.37	0.48
Serum calcium (mg/dL)	9.13±0.22	9.82±0.42	7.56	<0.001	9.07±0.23	9.22±0.37	1.65	0.6	<0.001
AST (IU/L)	20.62±3.31	21.11±4.32	2.38	0.88	21.69±3.35	21.89±5.24	0.92	0.44	0.52
ALT (IU/L)	20.91±3.34	20.25±2.67	−3.16	0.77	22.15±2.72	22.32±3.51	0.77	0.84	0.92
Urine specific gravity (g/mL)	1.07±0.42	1.03±0.33	−3.74	0.28	1.05±0.62	1.06±0.24	0.95	0.11	0.015
24-h urine volume (L)	1.72±0.23	1.74±0.35	1.16	0.32	1.81±0.13	1.79±0.31	−1.10	0.42	0.48
24-h urine calcium (mg)	163.33±12.49	151±14.83	7.55	0.02	158.69±18.22	157±20.24	−1.06	0.44	0.02
24-h urine magnesium (mg)	2.86±0.33	4.51±0.66	57.69	<0.001	2.94±0.38	3.11±0.54	5.78	0.72	<0.001

BUN=Blood urea nitrogen; AST=Aspartate transaminase; ALT=Alanine transaminase

DISCUSSION

Nephrolithiasis is a painful disease, resulting from solute supersaturation, crystal formation, aggregation, and retention in the collecting system.[6]

The current medications for nephrolithiasis have some limitations. Tamsulosin has no solving effects on kidney stones and only facilitates the excretion of stones. On the other hand, using thiazides, allopurinol, and citrate buffers for calcium kidney stones (unlike cystine and uric acid stones) does not dissolve existing stones. It only prevents the formation of new kidney stones.[20] The effective and safe formulation for the dissolution of calcium kidney stones is not known. If such a combination is discovered, a new horizon in the treatment of nephrolithiasis will appear.

Many medications for kidney/bladder stones have been reported in TPM pharmaceutical manuscripts. Rhazes described his methods for diagnosing and treating calculi in a book on urinary calculi.[21] Avicenna described kidney and bladder diseases in the chapter of his encyclopedia, "The Canon of Medicine."[22]

This study investigated the efficacy and safety of a traditional polyherbal product known as *Mofatet* powder used for kidney stones. To facilitate its use and increase the patient's compliance, uniformity of the preparation, and stability of the formulation, we aimed to reformulate the aqueous extract as a capsule using the freeze-drying technique.

There are several reports of renal protective effects of some of the ingredients of *Mofatet* powder. A study suggests that the methanolic extract of *C. pepo* L. could inhibit all stages of calcium oxalate stone formation, including nucleation, accumulation, and growth in the animal model of rats. Moreover, it could significantly reduce serum creatinine levels, BUN, and uric acid.[23]

Another study on *C. sativus* L. showed its nephroprotective effects by reducing serum creatinine, BUN, and lipid

peroxidation and increasing creatinine excretion and the activity of superoxide dismutase and catalase.[24]

There are also numerous reports of the ability of *T. terrestris* L. to dissolve kidney stones, which has been attributed to the ability of a protein isolated from it which convert oxalate to formic acid and carbon dioxide.[25] Moreover, studies show the protective effects of the *F. vulgare* Mill. aqueous extract on renal poisoning caused by cadmium chloride.[26]

Another study suggests *Pimpinella anisum* L. as a protective agent against epithelial and granular destruction and necrosis of renal cells caused by gentamicin.[27] In addition, the diuretic effects of *A. graveolens* L. have been considered a factor in the dissolution of calcium stones. Results of a clinical trial showed that daily consumption of two capsules of freeze-dried aqueous extract of *Mofatet* powder could significantly reduce the size of stones (by 60.73%) in the drug group ($P < 0.001$).[28]

Since the stones in the lower bridge of the kidney are not able to excrete spontaneously, the only way to excrete these stones is to dissolve and excrete them through urine. The reduction in the calcium excreted in the urine, and the specific gravity of the urine indicated the efficiency of the formulation in reducing the formation of supersaturation as an initiating factor in kidney stone formation.[29] Because urine magnesium is considered an inhibitor of the formation of oxalate calcium crystals, the increase in urinary magnesium in patients receiving the drug indicates one of the mechanisms of action of this product.[18,30]

CONCLUSION

This work evaluated the safety and efficacy of a traditional formulation for nephrolithiasis. Results of the study suggest that *Mofatet* powder is a safe and effective agent for the treatment of calcium stones. A significant reduction was observed in stone size after 5 weeks of treatment. No clinically significant adverse reactions were observed during the study. Further detailed *in vitro* and *in vivo* studies aimed at discovering the mechanism of action of this formulation, and clinical studies involving a larger population of patients will be necessary to explain and confirm the results obtained in the present study.

Data availability

Data are available on request. Please contact zarm@sums.ac.ir.

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Conflicts of interest

There are no conflicts of interest.

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