Original Article

Efficacy of an Oral Solution Containing Five Herbal Extracts in the Treatment of Urolithiasis: A Randomized, Single-blind, Placebo-controlled Clinical Trial

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ABSTRACT

Objective: The high prevalence of urolithiasis and its recurrence entail the preparation of an efficient drug with the least side effects. *Tribulus terrestris*, *Urtica dioica*, *Adiantum capillus-veneris*, *Stigma maydis* (corn silk), and *Cucumis melo* are herbal remedies utilized in traditional medicine for urolithiasis. This study aimed to assess the efficiency of these plants' extracts in treating urolithiasis. **Methods:** In a randomized, single-blind, placebo-controlled clinical trial, participants meeting inclusion criteria were randomly allocated to the drug (n = 27) and placebo (n = 27) groups to take herbal or placebo solutions, respectively, at a dose of 60 drops 3 times daily for 4 weeks with standard treatment. Before and after the intervention, 24-h urine volume and the quantities of calcium, sodium, citrate, oxalate, urea, creatinine, and uric acid in 24-h urine, and urinary pH were measured. The number and size (diameter in mm) of stones were determined by ultrasonography and recorded for each patient. **Findings:** Except for 24 h urine volume, other urinary parameters did not alter significantly at the end of the intervention compared to baseline. Furthermore, the two groups had no significant difference regarding these indices. Regarding stone parameters, the stone size decreased significantly in the drug group compared to the placebo group (P = 0.049). The number of cases with complete stone expulsion in the drug group was significantly higher than in the placebo group (12 cases vs. 4 cases, respectively, P = 0.017). **Conclusion:** Oral consumption of the herbal solution causes stone size reduction and stone expulsion in patients with urolithiasis.

Keywords: *Clinical trial, herbal solution, urolithiasis*

Introduction

Urolithiasis refers to the appearance of stones in the kidney, ureter, bladder, and/or urethra.[1] The prevalence of urolithiasis was around 5.2% in 1994,

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but it doubled by 2017.[2,3] A leading concern with urolithiasis is morbidity due to renal colic, which begins with severe and sudden pain. It has also been associated with sepsis and even death in severe cases resulting from infectious stones causing obstruction.[4] Hypercalciuria, hyperuricosuria, hyperoxaluria, hypocitraturia, and dehydration are risk factors for stone formation.[5,6] The high sodium concentration in the urine due to a high-salt diet can increase the risk of stone formation by increasing calcium secretion.[7] Consumption of animal proteins drives the secretion of sulfureous amino acids (e.g., cysteine and methionine), uric acid, and other acidic metabolites into the urine, making it acidic. As the pH of the urine decreases, the secretion of calcium and uric acid rises, and on the other hand, the secretion of citrate decreases, all of which enhance the risk of stone formation.[8]

Treatments for urolithiasis include pain relief in renal colic with nonsteroidal anti-inflammatory drugs and acetaminophen,[9,10] medical expulsive therapy with alpha-adrenoceptor antagonists (e.g., tamsulosin),[11] oral chemolysis (using potassium citrate or sodium bicarbonate),[12] and interventional measures such as extracorporeal shockwave lithotripsy (ESWL).[13] Chemolysis is correlated with gastrointestinal complications and intolerance of the patient due to bloating and diarrhea.[14] ESWL comes with some complications and side effects, including the traumatic influences of the waves on other organs and the kidneys, the retention of small stones and their potential to become the nucleus for new stones, decreased renal function, hypertension, severe hematuria, and infection.[15]

The high prevalence of urolithiasis and its recurrence constrain the provision of an effective drug with the least side effects. As stated, pharmacotherapy and surgery come with many side effects, while failing to diminish the risk of recurrence.[16]

Today, the WHO has included phytotherapy in its health programs.[17] Herbal treatment of urolithiasis is remarkable and has been practiced for a long time.[18] *Tribulus terrestris, Urtica dioica*, *Adiantum capillus-veneris*, *Stigma maydis* (corn silk), and *Cucumis melo* are herbal remedies utilized in traditional medicine.

T. terrestris exerts antispasmodic,[19] antidiuretic, and antiurolithiatic[20,21] effects. *U. dioica* inhibits the accumulation of calcium and oxalate and prevents the growth of urinary crystals due to having flavonoids (e.g., quercetin and kaempferol), anthocyanins, and saponins.[22,23] *A. capillus-veneris* inhibits urinary crystallization and decreases the number and size of crystals.[24] *S. maydis* has applications in treating urolithiasis due to its diuretic and kaliuretic effects.[25,26] Limited studies have confirmed the diuretic and antiurolithiasis effects of *C. melo*.[27,28]

Considering the consumption of these plants in traditional medicine for removing urinary stones and since no clinical research has been conducted on them regarding this effect, the present study attempted to clinically investigate the potential effects of an oral solution containing the extracts of these plants in the treatment of urolithiasis.

Methods

Plant samples were purchased from a trustworthy supplier and were identified and approved by an expert in the Research Center of Tabib Daru Company (Kashan, Iran). The hydroalcoholic extract of these plants was prepared using the percolation method and formulated in the form of oral drops at Tabib Daru Company. The plant extract was standardized based on the content of total phenolic compounds.

Each component of the formulation was prepared as an oral solution based on the allowable range of each plant and was standardized considering the content of total phenolic compounds per milliliter of the solution. The extracts of *T. terrestris* leaf, *U. dioica* root, *A. capillus-veneris* leaf, *S. maydis* (silks), and *C. melo* seeds were formulated as oral drop solution. The final product was standardized according to 1.2 mg phenolic content per mL of oral solution. The placebo solution was prepared using the same solvents utilized to produce the drug solution, and both product types were prepared in the same glass bottles with similar labels. Each bottle was given a numeric code according to its content by the company.

This randomized, single-blind, placebo-controlled clinical trial was conducted from October 2019 to October 2020. The study was registered with the code IRCT20150721023282N4 in the IRCT (Iranian Registry of Clinical Trials). The study protocol was approved with the ethics code IR.MUI.RESEARCH.REC.1398.383 by the Ethics Committee of Isfahan University of Medical Science after reviewing the documents on the safety of plant extracts performed by the Toxicology Department of Tehran University of Medical Sciences. All participants were asked to sign the written consent form.

The patients were selected from those referred to either the Nephrology or Urology clinics of Al-Zahra Hospital, affiliated with Isfahan University of Medical

Science, Isfahan, Iran. The inclusion criteria were (1) age of 18 years and older; (2) having symptomatic or asymptomatic kidney stone; and (3) the stone size of 10 mm or less (the largest diameter). The exclusion criteria were (1) having malignancy with bone metastasis; (2) having hyperthyroidism, hyperparathyroidism, psychosis, or impaired renal function (serum creatinine above 1.4 mg/dL); (3) structural disorder of the urinary tract or active urinary tract infection (UTI); (4) having uncontrolled gout or hyperuricemia; (5) consumption of other traditional remedies and supplements utilized in the treatment of urolithiasis within the last week; (6) pregnancy; and (7) lactation.

Participants who met the inclusion criteria were randomly allocated into two groups: drug (herbal extract) and placebo. Patients in both groups were instructed to drink adequate fluids to maintain a urinary volume of at least 2 L/day and avoid consuming other traditional products and complementary medications for treating urolithiasis. Furthermore, they were given nutritional recommendations, including salt and protein intake restrictions. Before the intervention, 24-h urine samples were taken from the patients of both groups to measure urine volume and urinary concentrations of calcium, sodium, citrate, oxalate, urea, creatinine, uric acid, and urinary pH. In addition, the number and size of stones (in mm) in each patient were determined by a radiologist/sonographer using ultrasonography at the hospital. In cases where the patient had more than one stone in one or two kidneys, the sum of stone sizes was calculated. For the patients in the drug group, the herbal solution with a dose of 60 drops 3 times a day was prescribed for 4 weeks with standard treatment depending on the type of stone and the opinion of the treating physician. For participants in the placebo group, the placebo solution with the same dose and duration was prescribed along with the standard treatment. For randomizing and blinding purposes, the pharmaceutical company coded the drug and placebo bottles during the preparation phase. When patients signed the consent form, a bottle was given to them randomly, and the code was recorded on the patient consent form. At the end of the sampling phase and when the results were obtained, the recorded codes of patients were decoded, and the type of intervention (drug vs. placebo) was determined for each patient. The prescribing physician, data collecting person, and the laboratory staff were unaware of the type of intervention. Furthermore, the specified codes were only accessible to a person from the pharmaceutical company who was not involved in the study process.

At the end of the intervention, all of the parameters mentioned above were measured and re-recorded. Moreover, the number of patients with a total stone expulsion in each group was recorded. A complete expulsion of the stone was confirmed by the patient's report regarding direct observation during urination with or without taking and holding the stone (s) and by comparing the ultrasonography results obtained at the start and end of the intervention. Of note, all ultrasonography results were interpreted by one radiologist/sonographer.

In addition, during the study, any potential adverse effects were recorded by asking the patients through telephone contact.

The primary outcome measures were the change of the mentioned urinary and stone parameters at the end of the intervention and their comparison between the two groups. The secondary outcome measures were the number of cases with complete stone expulsion at the end of the intervention and its comparison between the groups, the type of any possible reported adverse effects, and its rate.

The following equation was used to measure the sample size, considering the primary variable of this study (i.e., renal stone size), which is a continuous quantitative variable. In this work, the α and β errors were considered 5% and 20%, respectively. Accordingly, $Z_{\alpha/2}$ and Z_{β} were determined to be 1.65 and 0.842, respectively. According to a previous study, the minimum significant difference (d) was estimated at 6.77. According to the same study, the standard deviation was 6.20.[29]

$$n = \frac{(Z_{\alpha/2} + Z_{\beta})^2 \times 2 \times (\mathrm{SD})^2}{(d)^2}$$

Therefore, in each group, the sample size was at least 11 patients.

Data were analyzed using IBM SPSS Statistics 24 software (SPSS Inc., Chicago, IL, USA). The pattern of data distribution was determined using the Kolmogorov–Smirnov test. The Chi-square test was applied to compare the gender and the number of cases of complete stone expulsion between the two groups. Paired samples *t*-test or Wilcoxon signed-rank test, whichever is appropriate, were employed to compare quantitative data at the start and end of the intervention in each group. Independent samples *t*-test or Mann–Whitney *U*-tests, whichever is appropriate, were used to compare the values between the two groups at each time point. $P < 0.05$ was considered statistically significant.

Results

During this study, 109 patients were evaluated, of which 89 met the inclusion criteria. A total of 62 patients consented to participate, of which five from the drug group and three from the placebo group were excluded from the study for various reasons, including no cooperation during treatment, failure to observe the frequency of drug consumption, and failure to perform timely urine and ultrasound tests. Finally, 54 patients finished the study, including 27 patients in both drug and placebo groups [Figure 1]. Table 1 shows the demographic and clinical characteristics of the patients attending the study. The table shows no significant difference between the two groups regarding these parameters at the start of the study.

Table 2 provides the comparison of urine biochemical indices between drug and placebo groups before and after the intervention. As shown, there was no significant difference between the two groups in any of the indicators at the end of the intervention. Moreover, except for 24-h urine volume, there was no significant change in other indicators at the end of the intervention, as compared to the start point. For 24-h urine volume, though there was a significant increase in the drug group, this change was not significant compared to the placebo group.

Table 3 provides the comparison of stone indices and the rate of complete stone expulsion between the drug and placebo groups. From the table, though there was a significant decrease in the number of stones in the drug group (P = 0.009), this change was not significant at the end of the intervention compared to the placebo (P = 0.093). Furthermore, as seen, the stone size was reduced in both groups, with the percentage of reduction being significantly higher in the drug group than in the placebo group (P = 0.049). A comparison of the two groups in terms of the rate of complete stone expulsion at the end of intervention showed a significantly higher rate in the drug group compared to the placebo (44.44% vs. 14.81%, respectively; P = 0.017).

During the study, only two patients in the drug group complained of heartburn, which both resolved by prescribing the oral drops with meals.

Discussion

In this study, the percentage of stone size reduction was significant in the group receiving herbal drops compared to the placebo group. Furthermore, during the study, the cases of complete stone expulsion in patients receiving herbal drops were significantly higher than in the placebo group. Furthermore, there was more increase of urine volume in the herbal drug group, though insignificant compared to placebo, indicating the potential diuretic effect of this herbal mixture. Of note, although the reduction of stone number by the herbal drug was not statistically significant compared with the placebo, its significant decrease compared to the baseline shows that

Table 1: Baseline demographic and clinical parameters of study patients

Variable	Drug group (n=27)	Placebo group (n=27)	P
Age (years)	53.22 (12.69)	49.89 (13.31)	0.351[a]
Gender, *n* (%)			
Male	18 (66.67)	13 (48.15)	0.169[b]
Female	9 (33.33)	14 (51.85)	
Metabolic abnormalities, *n* (%)			
Hypercalciuria	0	1 (3.7)	0.562[b]
Hypocitraturia	4 (14.8)	2 (7.4)	
Hyperoxaluria	4 (14.8)	2 (7.4)	
Hyperuricosuria	3 (11.2)	2 (7.4)	
Urine volume (mL)	1395.18 (683.66)	1283.33 (603.99)	0.615[c]
Urine calcium (mg/24 h)	118.71 (65.01)	138.95 (126.96)	0.796[c]
Urine sodium (mEq/24 h)	152.36 (74.25)	147.99 (59.47)	0.812[a]
Urine citrate (mg/24 h)	527.42 (271.53)	499.12 (213.49)	0.672[a]
Urine oxalate (mg/24 h)	33.02 (17.50)	34.63 (20.95)	0.762[a]
Urine urea (mg/24 h)	17.48 (6.23)	15.53 (5.38)	0.451[c]
Urine creatinine (mg/24 h)	1136.72 (313.82)	1076.76 (260.51)	0.454[a]
Urine uric acid (mg/24 h)	507.10 (199.30)	459.53 (156.83)	0.344[a]
Urine pH	5.31 (0.55)	5.30 (0.41)	0.512[c]
Number of stones	1.7 (1.03)	1.96 (1.25)	0.482[c]
Stone size (mm)	6.78 (5.47)	7.56 (6.06)	0.482[c]

The values of quantitative parameters are presented as mean (SD). [a]Independent samples *t*-test, [b]Chi-square test, [c]Mann–Whitney *U*-test. SD=Standard deviation

a longer duration of intervention and/or use of higher product doses might result in a more substantial effect. Overall, these results show the positive therapeutic effects of the herbal product on nephrolithiasis.

The herbal medicine studied in this work contained five herbal extracts. Although the pharmacological and/or clinical effects of each component have been studied separately, to the best of our knowledge, this study is the first clinical investigation of the influence of such a compound on kidney stones and 24 h urine indices.

Table 2: The change of urinary parameters during the study and their comparison between the study groups

Variable	Time	Drug group (*n*=27)	Placebo group (*n*=27)	*P*
Urine volume (mL)	Baseline	1395.18 (683.66)	1283.33 (603.99)	0.615[a]
	End	1731.48 (689.36)	1511.53 (546.50)	0.236[a]
	P	0.003[c]	0.042[c]	
Urine calcium (mg/24 h)	Baseline	118.75 (65.01)	138.95 (126.96)	0.769[a]
	End	137.25 (56.35)	127.84 (92.19)	0.137[a]
	P	0.127[d]	0.527[c]	
Urine sodium (mEq/24 h)	Baseline	152.36 (74.25)	147.99 (59.47)	0.812[b]
	End	158.10 (73.61)	141.28 (47.33)	0.329[b]
	P	0.729[d]	0.646[d]	
Urine citrate (mg/24 h)	Baseline	527.42 (271.53)	499.12 (213.49)	0.672[b]
	End	558.23 (216.13)	504.10 (314.13)	0.152[a]
	P	0.810[d]	0.638[c]	
Urine oxalate (mg/24 h)	Baseline	33.02 (17.50)	34.63 (20.95)	0.762[b]
	End	31.74 (15.28)	33.84 (17.38)	0.520[b]
	P	0.761[d]	0.931[d]	
Urine urea (mg/24 h)	Baseline	17.48 (6.23)	15.53 (5.38)	0.451[a]
	End	17.11 (5.06)	15.94 (3.80)	0.437[a]
	P	0.784[c]	0.981[c]	
Urine creatinine (mg/24 h)	Baseline	1136.72 (313.81)	1076.76 (260.51)	0.454[b]
	End	1216.77 (399.84)	1142.26 (354.15)	0.423[a]
	P	0.333[d]	0.288[c]	
Urine uric acid (mg/24 h)	Baseline	507.10 (199.30)	459.53 (156.83)	0.344[b]
	End	498.94 (170.03)	480.23 (186.31)	0.661[b]
	P	0.849[d]	0.593[d]	
Urine pH	Baseline	5.31 (0.55)	5.20 (0.41)	0.512[a]
	End	5.28 (0.49)	5.29 (0.46)	0.891[a]
	P	1.00[c]	0.066[c]	

The values are presented as mean (SD). [a]Mann–Whitney *U*-test, [b]Independent samples *t*-test, [c]Wilcoxon signed-rank test, [d]Paired samples *t*-test. SD=Standard deviation

In 2019, the study of Kaushik *et al*. on rats with induced hyperoxaluria and crystalluria showed that the aqueous extract of *T. terrestris* reduces the size and number of urinary crystals in a dose-dependent manner.[30] Zhang *et al*. investigated male rats with calcium oxalate stones and found that consuming hydroalcoholic extract of *U. dioica* root can reduce urinary calcium, oxalate, and creatinine. In addition, histological studies of the kidneys showed decreased calcium oxalate deposition.[22] In the study of Ahmed *et al*., the effect of hydroalcoholic extract of *A. capillus-veneris* on kidney calcium oxalate stones was investigated. According to the results, the extract significantly lowered blood concentration of calcium and urea, and microscopic urine tests showed a decrease in the number of crystals.[31]

As discussed, based on our literature review, this work is the first clinical study on this topic. For *T. terrestris*, studies have covered only sexual disorders in men and women.[32,33] For *U. dioica*, research has been conducted on diabetes,[34] benign prostatic hyperplasia,[35] and allergic rhinitis.[36] For *S. maydis*, studies have been focused on blood pressure,[37] hyperlipidemia,[38] and UTI.[39]

As mentioned previously, herbs with several pharmacological effects can efficiently treat urolithiasis, though the mechanism of action is unclear. These pharmacological consequences include diuretic, anti-inflammatory, antispasmodic, antioxidant, pH-altering, and urinary ion-concentrating effects.[40]

In this study, urinary indices were evaluated using a 24 h urine test to find metabolic disorders and possible changes in the parameters with the herbal solution. The abnormality of some of these parameters (e.g., hypercalciuria, hyperoxaluria, hyperuricosuria, and hypocitraturia) has been accepted as a risk factor for urolithiasis. Sodium, as an indicator of salt intake in the diet, was evaluated as one of the primary nuclei of stone formation. Urea and uric acid were further assessed as indicators of dietary protein intake, and creatinine was used to indicate the accuracy of the urinary test.[41,42]

In this study, no significant difference was observed in the urine indices between the drug and placebo groups;

Table 3: The change of stone parameters during the study and their comparison between the study groups

Variable	Time	Drug group (*n*=27)	Placebo group (*n*=27)	*P*
Number of stones, mean (SD)	Baseline	1.70 (1.03)	1.96 (1.25)	0.482[a]
	End	1.11 (1.25)	1.74 (1.58)	0.093[a]
	P	0.009[c]	0.376[c]	
Percent of change in stone size, mean (SD)	End	−37.60 (74.77)	−7.55 (69.47)	0.049[a]
Complete stone expulsion, number of patients (%)	End	12 (44.44)	4 (14.81)	0.017[b]

[a]Mann–Whitney *U*-test, [b]Chi-square test, [c]Wilcoxon signed-rank test. SD=Standard deviation

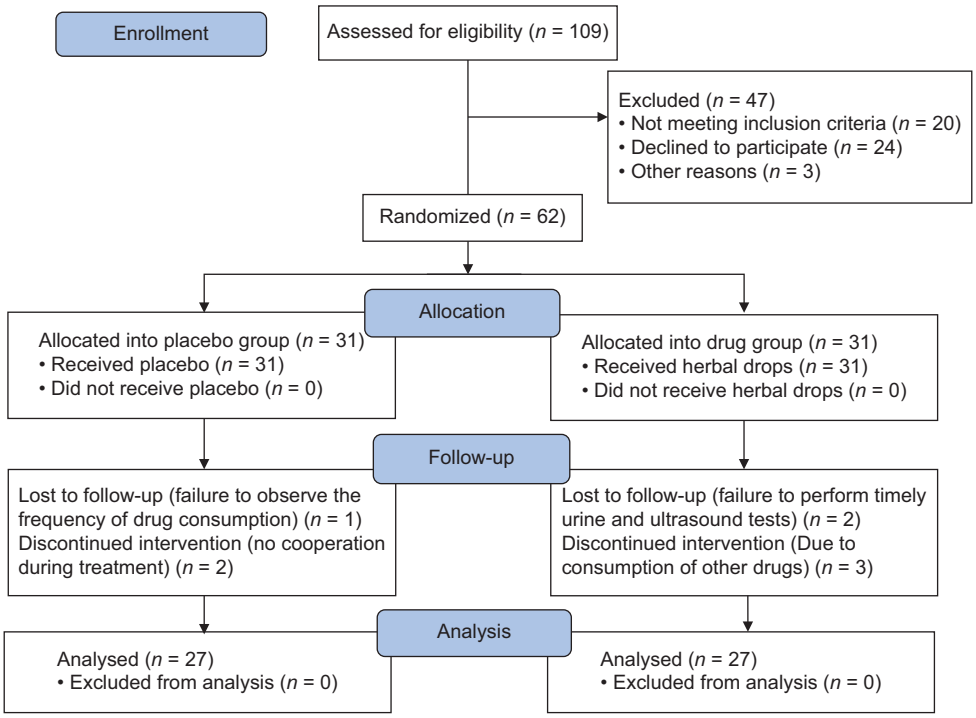

Figure 1: Flow chart of enrollment and allocation of participants and study design

however, a significant increase in the urine volume in the drug group can be promising for the diuretic effect of the drug at higher doses. Some animal studies have investigated the diuretic effect of *T. terrestris*, *U. dioica*, and *S. maydis*. Al-Ali *et al*. study evaluated and compared the diuretic effect of *T. terrestris*, *S. maydis*, and furosemide on 30 rats. From the results, the extract of fruits and leaves of *T. terrestris* at a dose of 5 mg/kg resulted in an 189% increase in urine volume within 24 h, which was slightly higher than the diuretic effect of furosemide (179%). Furthermore, although *S. maydis* extract did not provide significant results when tested alone, it resulted in a 100% increase in urine volume when used with *T. terrestris* extract.[43] The diuretic effect of *U. dioica* has also been shown.[44] Therefore, one of the likely mechanisms of the effectiveness of the herbal solution in our study may be the diuretic effect mediated by *T. terrestris*, *U. dioica*, and *S. maydis*, which is consistent with a significant increase in urine volume in the drug group.

In several studies, the role of oxidative stress and inflammation as important factors in the pathogenesis of urolithiasis has been discussed.[45-47] Contact of kidney cells with calcium oxalate crystals leads to the production of reactive oxygen species and the onset of oxidative stress in the renal tubules, which leads to tubular damage and inflammation. Any damage and inflammation begin with accumulating calcium oxalate crystals and forming stones.[48] Therefore, recent studies indicate the advantage of antioxidants in inhibiting and treating urolithiasis.[49] Plants that contain phenolic compounds and are especially rich in flavonoids can be effective in this regard.[50] *T. terrestris*,[51,52] *U. dioica*,[53] *A. capillus-veneris*,[54] *S. maydis*,[55] and *C. melo*[56] are all rich in phenolic and flavonoid compounds, and their antioxidant properties have been confirmed, which can be one of the reasons for the effectiveness of the herbal solution used in our study in the treatment of urolithiasis.

Regarding the greater number of participants who released renal stones in the drug group in our study, another possible mechanism of the observed effects of the herbal product could be an antispasmodic effect on the smooth muscles of the urinary tract. The antispasmodic effects of *A. capillus-veneris* and *T. terrestris* have been shown previously.[19,57]

In general, given the high prevalence of urolithiasis and limited effective treatment options for it, and considering the results of this study, the use of an herbal solution containing the mentioned plant extracts can be viewed as a potential treatment for this disorder. This entails more research to determine the product's optimum concentration and the ideal consumption duration.

This study's main limitations were the short intervention duration and low sample size, mainly due to the COVID-19 pandemic. However, it is a well-controlled clinical study determining the good

potential of an herbal compound for improving urolithiasis treatment.

Consumption of herbal solutions containing the extracts of *T. terrestris*, *U. dioica*, *A. capillus-veneris*, *S. maydis*, and *C. melo* seeds causes stone size reduction and stone expulsion in patients with urolithiasis. Therefore, it can potentially be considered a supplemental treatment for this disorder.

Authors' Contribution

R. Soltani designed the study, interpreted the results, and performed the statistical analysis. S. Samandarian and A. Mohsenzadeh collected the patients' data and drafted the manuscript. V. Hajhashemi gave the study concept and interpreted the data. M. Dehghani and M. Matinfar selected the patients and interpreted the data. M. Mahboubi prepared the herbal and placebo solutions and standardized the herbal one. All authors approved the final manuscript.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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