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The effects of *Portulaca oleracea* extract on 24-hour urine indices in patients with renal stone: A double-blind randomized placebo-controlled clinical trial

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ABSTRACT

Introduction: *Portulaca oleracea*, or purslane, is a medicinal plant used in traditional medicine, according to its various medical properties, as well as its potential antioxidant and anti-inflammatory properties.

Objectives: The present study aimed to investigate the efficacy of *P. oleracea* powder on 24-hour urine indices in patients with nephrolithiasis and normal kidney function.

Patients and Methods: In this randomized clinical trial, eligible patients with nephrolithiasis were randomly assigned to receive *P. oleracea* or placebo capsules once daily for eight weeks. Twenty-four-hour urine indices, along with serum electrolytes, inflammatory and lipid components were measured, then compared between the two groups at baseline and the end of the trial.

Results: A total of 54 patients, including 28 in *P. oleracea* and 26 in the control groups, were assigned. Their mean age was 42.2 ± 9.8 years; there was no statistically significant difference between the mean age of the *P. oleracea* and placebo groups (42.1years versus 42.2 years, respectively; $P>0.05$). After eight weeks, the mean urine citrate level in the *Portulaca oleracea* subjects (674.82 ± 94.56 mg/24 h) was significantly higher than placebo group subjects (579.19 ± 85.06 mg/24 h; $P<0.01$). In addition, the mean urine calcium level in the *P. oleracea* group (176.32 ± 27.40 mg/24 h) was significantly lower compared to the control group (194.26 ± 25.17 mg/24 h; $P=0.016$). Within the groups, analysis revealed that in subjects in *P. oleracea* and control groups, mean serum triglyceride (TG) decreased after intervention ($P=0.01$ and $P=0.02$, respectively), as well as mean urine citrate level ($P<0.01$, $P=0.01$, respectively).

Conclusion: The findings show that *P. oleracea* may be proposed as a medicinal plant that has a preventive effect on kidney stone formation by increasing urine citrate and decreasing urine calcium level.

Trial Registration: The trial protocol was approved by the Iranian Registry of Clinical Trials (identifier: IRCT20170725035305N4; https://en.irct.ir/trial/42388, ethical code; IR.SBMU.MSP.REC.1398.538).

Clinical Trial

Introduction

Nephrolithiasis, one of the most common conditions affecting the urinary system, has been reported with an occurrence rate of about 12% worldwide (1). Kidney stones are categorized based on their components. They may comprise uric acid, calcium oxalate, calcium phosphate, cysteine, struvite, or a mixture of the mentioned components (2). Physicochemical changes and urine saturation are involved in forming kidney stones (3). Lithotripsy, flexible or rigid ureteroscopy, percutaneous nephrolithotomy, and, in selected cases, a laparoscopic approach are invasive procedures currently used for kidney stone management (4). In addition to conventional treatments for nephrolithiasis, herbal treatments have

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Implication for health policy/practice/research/medical education:
Portulaca oleracea is used in traditional medicine as a medicinal plant. According to its various medical properties, potential antioxidant and anti-inflammatory properties, the present study aimed to investigate the efficacy of *P. oleracea* powder on 24-hour urine indices in patients with nephrolithiasis and normal kidney function. The findings show that *P. oleracea* did not significantly affect urine creatinine levels. However, it significantly increased urine citrate levels and decreased urine calcium levels, which are common risk factors for nephrolithiasis. Therefore, *P. oleracea* may be proposed as a medicinal plant that has a preventive effect on kidney stone formation, though more studies are recommended to evaluate its safety and efficacy.
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long been used worldwide (5). *Portulaca oleracea* is an herbaceous succulent annual plant from the Portulacaceae family (6). *P. oleracea* is among the most medicinal plants used and has been named "Global Panacea" by the World Health Organization (7). It is grown in the tropical and subtropical areas of the world and used in different regions, including several parts of the United States, as a potherb or as an additive to salads or soups in the Mediterranean and tropical countries of Asia, as well as in Chinese traditional medicine (8-10). In European countries like Italy, Turkey, and Greece, *P. oleracea* has been used for medical conditions like headaches, stomach and kidney pains, intestinal worms, dysentery, urogenital infections, urinary inflammations, scurvy, or fever (11-13). *P. oleracea* is also commonly named Purslane and may be a source of ω-3 fatty acids, alfa-tocopherol, carotene, glutathione, and antioxidants (14).

Furthermore, this plant provides a source of potassium, calcium, magnesium, and phosphorus (15). Some studies showed properties of *P. oleracea* as a muscle-relaxant or a contraceptive agent, and also a herbal medicine preventing heart attacks and improving immune system (16). Likewise, the ability of inflammation decrement and protection from ischemia and reperfusion injuries has been proposed for this medicinal plant (17). However, its mechanism of action still needs to be clarified. Some studies reported a protective effect of *P. oleracea* against renal failure (18). Besides, it may be useful as an antioxidant and regulate the apoptosis in the kidney (19,20). Although various studies have indicated the different beneficial effects of *P. oleracea*, the findings of its effects on urine indices in individuals are limited. On the other hand, no clinically important adverse events have been reported in studies so far (21,22).

Objectives

This study aims to evaluate the efficacy of *P. oleracea* powder on 24-hour urine indices, serum electrolytes, and inflammatory and lipid components in patients with nephrolithiasis and normal kidney function.

Patients and Methods

Collection of samples

This single-center randomized, double-blind clinical trial was conducted in Shahid Modarres educational hospital, Shahid Beheshti university of medical sciences, Tehran, Iran.

In our study, the patients were randomly assigned to the *P. oleracea* or placebo groups. Eligible patients with a known history of renal stones were enrolled. Inclusion criteria were; 1) age from 18 to 65 years old, 2) having normal kidney function defined as normal estimated glomerular filtration rate (eGFR >90 mL/min/1.73 m^2), and 3) documented history of renal stone. Exclusion criteria were patients with diabetes, hypersensitivity to any of the active principles or excipients of the compound, pregnancy and lactation, positive urine culture, known urological and non-urological malignancy, taking angiotensin II inhibitors, and patients having cold symptoms (including headaches, sore throat, coughs, rhinorrhea, or fever).

At baseline, 57 patients were randomly grouped as follows: 1) *P. oleracea* group consisting of 31 patients randomly allocated to receive capsules made up of 2 g of *P. oleracea* and 0.5 g of brown sugar, once daily for eight weeks, 2) placebo group consisting of 26 participants to receive placebo capsules made up of 2 g of starch powder and 0.5 g brown sugar, once daily for eight weeks. The capsules were prescribed with an empty stomach in the morning, one hour before breakfast.

A balanced block randomization method was conducted, and the block size was four. Then, the allocation sequence was determined using computer-generated random numbers. Medicines containing *P. oleracea* powder or placebo having the same shape and color were numbered with a code in sealed envelopes. Each coded prepared medication was labeled from one to 57. The patients were allocated into two groups; group 1 received *P. oleracea*, and group 2 received a placebo. Both groups were identical regarding comorbid conditions and characteristics. The control group was assigned to "A" and the intervention group to "B". The two groups were divided into six blocks and then put together by computer and provided a chain of randomized groups. Eventually, the patients enter these groups in order to time of entry. Then, the patients enter these groups in order of entry. During the study period, a nurse was responsible for distributing labeled drugs among participants and collecting all the data. The investigators, nurses, participants, laboratory staff, and supervisors were all blinded to treatment assignment and lab data measurements during the

study. All participants received the same dietary regimen based on low animal-source protein and more fruits and vegetables prescribed by the nutritionist over the study period. In addition, the dietary regimen was limited to low-sugar foods and drinks. Participants were followed up by the mentioned expert nutritionist weekly by phone for adherence to the dietary regimen. In the *P. oleracea* group, three participants were excluded due to loss of follow-up. Therefore, 54 participants, including 28 in *P. oleracea* and 26 in the placebo group, were analyzed.

Patients' compliance

At the beginning of the trial, one pack containing 56 capsules was given to each study participant. Patients' compliance was assessed once a week by phone call to ensure whether they regularly received their daily pearls.

Outcome measurement

Blood samples were collected from the antecubital vein, and 24-hour urine samples were collected from all participants at baseline and at the end of the trial after eight weeks. For the primary outcomes, serum potassium (K) level, serum sodium (Na) level, 24-hour urine uric acid, 24-hour urine citrate, 24-hour urine calcium, 24-hour urine creatinine (Cr), and 24-hour urine sodium was assessed. For the secondary outcomes, serum triglyceride (TG) level, serum total cholesterol level, erythrocyte sedimentation rate (ESR), and serum urea level were calculated.

Statistical analysis

The intention-to-treat method was conducted for statistical analysis, and all randomized participants enrolled in the study were included for analysis. Descriptive statistics were carried out for each variable. Quantitative results were presented as mean ± SD, while qualitative results were presented as frequencies. The two-sample *t* test was used to compare mean amounts of parameters between trial groups. Proportions for the two groups were compared using the chi-squared test. Meanwhile paired t-test was employed to compare the results before and after the trial. SPSS Statistical software package (SPSS, Inc., Chicago, IL, USA), version 22.0, and MedCalc software were utilized for statistical analyses. $P < 0.05$ was considered statistically significant.

Results

A total of 54 patients were included in this trial consisting

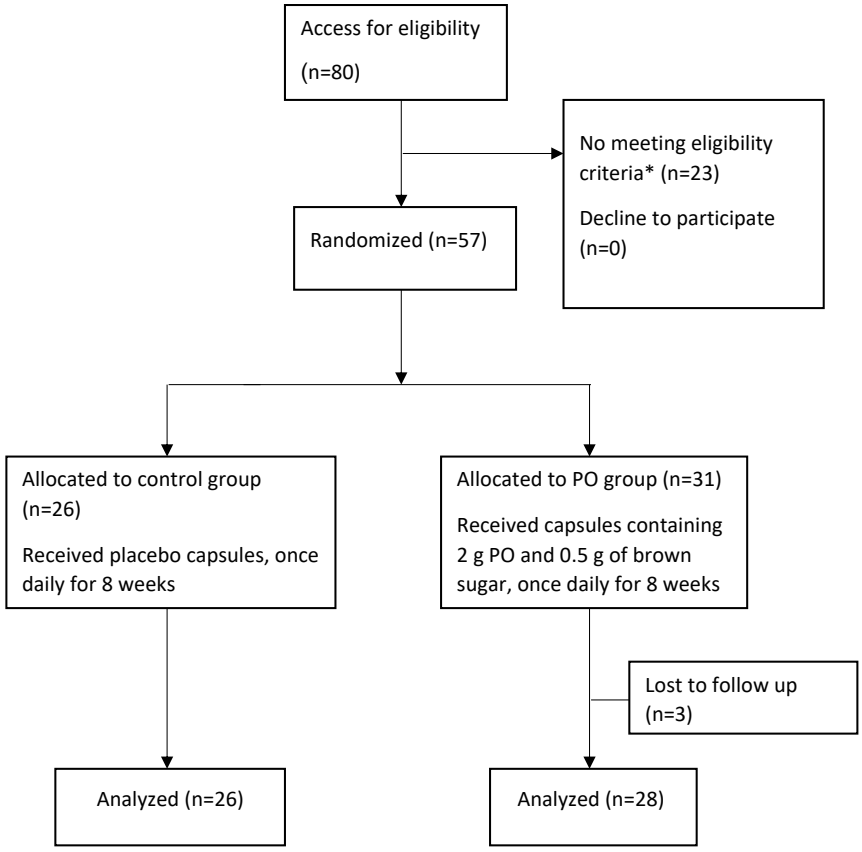

Figure 1. Flow diagram of the study. * Inclusion criteria were; 1) age from 18 to 65 years old, 2) having normal kidney function defined as normal estimated glomerular filtration rate (eGFR more than 90 mL/min/1.73 m^2), and 3) documented history of renal stone. Exclusion criteria were patients with diabetes, hypersensitivity to any of the active principles or excipients of the compound, pregnancy and lactation, positive urine culture, known urological and non-urological malignancy, use of angiotensin II inhibitors, and patients having cold symptoms (including headaches, sore throat, coughs, rhinorrhea, or fever). PO: *Portulaca oleracea*.

of 33 males (61.1%) and 21 (38.9 %) females (Figure 1). Twenty-eight participants were assigned to the *P. oleracea* group [18 males (64.3%)], and 26 participants to the control groups [15 men (57.7%)]. Their mean age was 42.2±9.8 years; there was no statistically significant difference between the mean age of *P. oleracea* and placebo group (42.1 years versus 42.2 years, respectively).

Regarding baseline serum and urine laboratory parameters, no statistically significant differences were seen except for the erythrocyte sedimentation rate (ESR) level being significantly higher in the *P. oleracea* group compared to placebo (25.32 ± 7.07 mm/h versus 20.03 ± 5.43 mm/h, respectively, P = 0.03). Besides, there were other baseline of laboratory performance between the two groups (Table 1).

After eight weeks, the mean urine citrate level in the *P. oleracea* subjects (674.82 ± 94.56 mg/24 h) was significantly higher than placebo group subjects (579.19 ± 85.06 mg/24 h; $P < 0.01$). In addition, the mean urine calcium level in the *P. oleracea* group (176.32 ± 27.40 mg/24 h) was significantly lower compared to the control group (194.26 ± 25.17 mg/24 h; $P = 0.016$). In this study we found that the mean ESR level was significantly higher in *P. oleracea* group at the end of the trial (22.03 ± 5.51 mm/h versus 17.61 ± 3.44 mm/h respectively; $P < 0.01$; Table 2).

As shown in Table 3, within-groups analysis revealed that in subjects in *P. oleracea* and control groups, mean serum triglyceride decreased after intervention ($P = 0.01$ and $P = 0.02$, respectively), as well as mean urine citrate level ($P < 0.01$, $P = 0.01$, respectively). However, in both *P. oleracea* and placebo groups mean ESR level decreased significantly after intervention ($P = 0.001$ and $P = 0.01$, respectively). In contrast, significant decreases in the mean urine calcium ($P < 0.01$), the mean serum total cholesterol level ($P = 0.02$), and the mean serum urea ($P = 0.032$) were only seen in *P. oleracea* group. Other findings showed the decrease in serum level of potassium in placebo group ($P = 0.004$).

Table 1. Comparison of baseline serum and urine laboratory parameters between trial groups

Parameters	PO group	Placebo group	*P* value
	Mean ± SD	Mean ± SD	
Serum Na (mEq/L)	139.07±2.22	138.19±2.43	0.17
Serum K (mEq/L)	4.30±0.40	4.32±0.44	0.84
Serum TG (mg/dL)	230.07±28.22	226.07±18.78	0.54
Serum total cholesterol (mg/dL)	206.21±28.22	203.65±25.31	0.74
Serum urea (mg/dL)	40.35±4.94	39.34±3.6	0.40
ESR (mm/h)	25.32±7.07	20.03±5.43	0.03
Urine Cr (mg/kg/24 h)	20.39±1.64	20.80±1.89	0.39
Urine uric acid (mg/24 h)	543.89±68.80	556.57±52.42	0.45
Urine citrate (mg/24 h)	511.71±76.85	539.57±87.39	0.21
Urine Ca (mg/24 h)	196.64±28.14	200.80±29.41	0.59
Urine Na (mEq/24 h)	136.25±31.63	122.15±27.32	0.08

PO: *Portulaca oleracea*, TG: triglyceride, ESR: estimated sedimentation rate, Cr: creatinine.

Table 2. Comparison of Serum and urine laboratory parameters between trial groups after intervention

Parameters	PO group	Placebo group	*P* value
	Mean ± SD	Mean ± SD	
Serum Na (mEq/L)	139.25±2.02	138.84±2.14	0.48
Serum K (mEq/L)	3.94±1.15	3.25±1.82	0.10
Serum TG (mg/dL)	217.39±13.87	216.19±15.46	0.83
Serum total cholesterol (mg/dL)	199.21±26.30	199.92±25.75	0.92
Serum urea (mg/dL)	38.21±5.73	38.96±3.54	0.56
ESR (mm/h)	22.03±5.51	17.61±3.44	0.00
Urine Cr (mg/kg/24 h)	20.42±1.68	20.61±1.69	0.68
Urine uric acid (mg/24 h)	518.21±64.87	560.38±44.89	0.07
Urine citrate (mg/24 h)	674.82±94.56	579.19±85.06	0.00
Urine Ca (mg/24 h)	176.32±27.40	194.26±25.17	0.02
Urine Na (mEq/24 h)	127.32±26.12	114.8±19.23	0.05

PO: *Portulaca oleracea*, TG: triglyceride, ESR: estimated sedimentation rate, Cr: creatinine.

Table 3. Comparison of baseline to post-intervention changes in serum and urine laboratory parameters of participants, separately in *Portulaca oleracea* and placebo groups

Parameters	PO group		*P* value[a]	Placebo group		*P* value[a]
	Pre-test	Post-test		Pre-test	Post-test	
	Mean±SD	Mean±SD		Mean±SD	Mean±SD	
Serum Na (mEq/L)	139.07±2.22	139.25±2.02	0.75	138.19±2.43	138.84±2.14	0.36
Serum K (mEq/L)	4.30±0.40	3.9±1.15	0.09	4.32±0.44	3.25±1.82	0.00
Serum TG (mg/dL)	230.07±28.22	217.03±13.87	0.01	226.07±18.78	216.19±15.46	0.02
Serum total cholesterol (mg/dL)	206.21±30.68	199.21±26.30	0.02	203.65±25.31	216.19±15.46	0.34
Serum urea (mg/dL)	40.35±4.94	38.21±5.73	0.03	39.34±3.66	38.96±3.54	0.63
ESR (mm/h)	25.32±7.07	22.03±5.51	0.00	20.03±5.43	17.61±3.44	0.01
Urine Cr (mg/kg/24 h)	20.39±1.64	20.42±1.68	0.93	20.80±1.89	20.61±1.69	0.75
Urine uric acid (mg/24 h)	543.89±68.80	518.21±64.87	0.01	556.57±52.42	560.38±44.89	0.47
Urine citrate (mg/24 h)	511.71±76.85	674.82±94.56	0.00	539.57 ±87.39	579.19±85.06	0.01
Urine Ca (mg/24 h)	196.64±28.14	176.32±27.40	0.00	200.80±29.41	194.26±25.17	0.27
Urine Na (mEq/24 h)	136.25±31.63	127.32±26.12	0.13	122.15±27.32	114.80±19.23	0.11

[a] Paired *t* test.
PO: *Portulaca oleracea*, TG: triglyceride, ESR: estimated sedimentation rate, Cr: creatinine.

Discussion

The findings of our study show that the mean urine citrate level was significantly higher in *P. oleracea* group compared to the placebo. Although the mean urine citrate level increased in *P. oleracea* and placebo groups, it was more prominent following *P. oleracea* administration. Likewise, the mean urine calcium and serum cholesterol levels decreased significantly following *P. oleracea* administration. It is worth mentioning that there was no significant difference in mean urine creatinine between the two groups.

Based on the results of previous studies, low excretion of citrate in urine may prone the patients to kidney stone formation and is known as a risk factor; so even up to about 68% had been reported for the prevalence of hypocitraturia in known cases of nephrolithiasis (23). The findings of our study showed a significantly higher urine citrate level in the *P. oleracea* group compared to placebo. Therefore, *P. oleracea* may be proposed for reducing the risk of nephrolithiasis.

As with other nephrolithiasis risk factors, hypercalciuria is known as the most common metabolic abnormality (24,25). In our study, the urine calcium level decreased significantly following *P. oleracea* administration, which proposes another mechanism for its potential protective effects against incident nephrolithiasis.

The results of previous studies showed that oxalate and calcium oxalate crystals are involved in the stone formation mechanism (26). Some other studies showed a relation between enhanced oxidative stress and calcium oxalate crystal formation leading to kidney stone (27,28). Therefore, preventing the oxidative processes may play an important role in preventing recurrent stone formation. In the same direction, there are different medicinal plants knowing to have important natural antioxidant properties (29).

In a previous study, following administration of *P. oleracea* with yogurt, a decrease in the soluble calcium oxalate levels from 53% to 10.7 % was reported (30). On the other hand, a case of acute kidney injury (AKI) was reported following eating a large amount of *P. oleracea*. Renal biopsy showed an acute tubulointerstitial injury and oxalate nephropathy was diagnosed. Since, the kidney function became back to normal following stopping eating *P. oleracea*, hydration, and hemodialysis (31). Therefore, the effect of *P. oleracea* on urine oxalate and calcium oxalate crystals remains controversial.

In another study, oral administration of *P. oleracea* improved kidney function tests by reducing the levels of urea, serum creatinine and blood urea nitrogen (32). *P. oleracea* is a main source of anti-oxidant vitamins such as ascorbic acid, β-carotene, α-tocopherol, and glutathione (16, 33); leading to potential antioxidant properties (34, 35). Therefore, *P. oleracea* may have effects on calcium oxalate crystal and kidney stone formation due to its anti-oxidant effects.

Some studies reported the effects of *P. oleracea* on decreasing thirsty state (36). On the other hand, previous finding showed that decreasing in fluid intake may lead to increased urine creatinine level (37). However, the urine creatinine level did not change in our study.

In another study that investigated the effects of *P. oleracea* on hyperlipidemia in rats, the cholesterol and triglyceride level decreased after treatment (38). In line with our results, we found cholesterol levels decreased iin *P. oleracea* group. TG level decreased in both of groups

but it was more prominent in *P. oleracea* group.

The main strength of our study is being the first, as far as we know, to evaluate the effects of *P. oleracea* extract on 24 -hour urine indices in patients with renal stone in a placebo-controlled clinical trial.

Conclusion

The findings show that although *P. oleracea* did not have significant effect on urine creatinine level. It may significantly increase urine citrate, and decrease urine calcium level as common risk factors of nephrolithiasis. Therefore, *P. oleracea* may be proposed as a medicinal plant having preventive effect on kidney stone formation and more studies are recommended to evaluate its safety and efficacy. Additionally, *P. oleracea* may have positive effects on lipid profile by decreasing serum total cholesterol level and more studies are recommended to evaluate its different properties on metabolic profiles including serum lipid.

Limitations of the study

The present study has several limitations. First, the effect of *P. oleracea* extract on thirst symptoms has not been evaluated. Secondly, since we followed the participants for only 8 weeks, we could not determine the burden of kidney stone.

Authors' contribution

Conceptualization: Amirhesam Alirezaei.
Data curation: Firoze Hatami.
Formal analysis: Seyed Behnaz Nouri.
Funding acquisition: Amirhesam Alirezaei
Investigation: Seyed Pedram Montazeri-Ghominezhad.
Methodology: Amirhesam Alirezaei.
Project administration: Amirhesam Alirezaei.
Resources: Seyed Pedram Montazeri-Ghominezhad.
Supervision: Amirhesam Alirezaei.
Validation: Seyed Amirhossein Fazeli.
Visualization: Amirhossein Miladipour.
Writing-original draft: Kimia Karimi Toudeshki.
Writing-review and editing: Seyed Amirhossein Fazeli, and Kimia Karimi Toudeshki.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

The study was conducted in accordance with the Declaration of Helsinki and was approved by the ethics committee of Shahid Beheshti University of Medical Sciences (Ethical code #IR.SBMU.MSP.REC.1398.538). It was also registered by the Iranian Registry of Clinical Trials (identifier: IRCT20170725035305N4; https://en.irct.ir/trial/42388). All patients provided signed informed consent after receiving explanations about the study's aim and methods. The authors ensured that ethical issues, such as plagiarism, data fabrication, and double publication, were completely observed.

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