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Research Journal of Pharmacognosy (RJP) 6(1), 2019: 35-42
Received: 19 May 2018
Accepted: 27 Aug 2018
Published online: 18 Dec 2018
DOI: 10.22127/rjp.2018.80369

Original article

Cicer arietinum in the Treatment of Small Renal Stones: a Double-Blind, Randomized and Placebo-Controlled Trial

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Abstract

Background and objectives: Urolithiasis is a common urological disorder. Based on the Persian medicine literatures, *Cicer arietinum* has a potential to dissolve renal stones. This study was designed to assess the efficacy and safety of *Cicer arietinum* in patients with renal stone.

Methods: The extract of *C. arietinum* seeds was spray dried. A randomized, double blind, placebo-controlled study was conducted on 74 patients with 6-10 mm renal stones in ultrasonography. Patients were randomly assigned to take 330 mg of *C. arietinum* extract or placebo capsules three times a day for 30 days. Complete stone dissolution and the change in stone size during the trial was evaluated by ultrasonography. To assess the efficacy and safety of *C. arietinum*, blood and urine biochemical parameters were checked at baseline and after the intervention. **Results:** In the *C. arietinum* group, complete stone dissolution occurred in 9 (23.7%) patients and reduce in stone size was observed in 17 (44.7%) patients while no response to treatment was observed in placebo group**.** The mean stone size was reduced from 7.15 ± 1.34 mm to 4.28 ± 3.09 mm in the *C. arietinum* group ($p<0.001$) and was increased from 7.08 ± 1.09 mm to 7.15 ±1.09 mm in the placebo group ($p=0.13$). The changes of the stone size were significantly higher in the drug consumer group ($p<0.001$). The changes of the urinary volume and magnesium level were significantly higher in the treatment group ($P=0.04$ and $P=0.02$, respectively). **Conclusion**: *Cicer arietinum* extract could be an effective and safe treatment option for patients with 6-10 mm renal stones.

Keywords: *Cicer arietinum*; clinical trial; Iranian traditional medicine; kidney calculi

Citation: Biglarkhani M, Amir Zargar MA, Hashem-Dabaghian F, Amini Behbahani F, Meyari A, Sadeghpour O. *Cicer arietinum* in the treatment of small renal stones: a double-blind, randomized and placebo-controlled trial. Res J Pharmacogn. 2019; 6(1): 35-42.

Introduction

Urolithiasis is the third most common urological affliction with high recurrence and considerable morbidity [1,2]. The prevalence and incidence of the problem is increasing worldwide [3]. The lifetime risk of developing urolithiasis is about 10-15% in the western world and 20-25% in the Middle East [4]. Seventy five to ninety percent of stones are composed of calcium oxalate and calcium phosphate. Stone formation is a complex process that occurs due to imbalance between promoters and inhibitors in the kidneys, ureters and/or bladder [2,5]. Treatment options vary

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from conservative follow up for asymptomatic and non-complicated patients with smaller than 1 cm size of stones to pharmacological and surgical interventions for larger and/or symptomatic and/or complicated stones [6]. Procedural treatment options are costly and may have some complications [7-9]. Conventional drug therapies are not completely effective and overuse of many synthetic drugs like diuretics and narcotic analgesics result in adverse reactions [10-12]. Therefore, researchers have shifted toward evaluating efficacy of anti-urolithiatics medicinal plants [5].

Cicer arietinum L. known as "chickpea" or "Bengal gram" in English and "Nokhod" in Persian, belongs to the Fabaceae family. It is grouped into two biotypes: Desi and Kabuli. Recent studies have shown *C. arietinum*, especially the Desi type, has several pharmacological effects and biological activities [13-18]. The biological effect of the Desi type of chickpea in kidney stones has been described in Persian medicine literatures such as "the Liber continent" [19] and "the Canon of medicine" [20]. Moreover, a recent animal study has shown that it has lithotriptic and diuretic effects in albino rats with no side effects or symptoms of toxicity [21]. The present double blind, randomized, placebo controlled trial was conducted to assess the efficacy and safety of *C. arietinum* in patients with the size of kidney stone between 6 to 10 mm.

Material and Methods

Ethical considerations

The trial was conducted according to 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 (CONSORT) [22]. Patients' personal information was kept confidential. The study protocol was reviewed and approved by the Ethical Committee of Iran University of Medical Sciences (registration number: IR.IUMS.REC 2016.9221309208). All participants signed a written informed consent before recruiting in the study.

Plant material, preparation of drug and placebo

Seeds of *C. arietinum* (Desi type) was purchased from a local market of medicinal plants in Hamedan, Iran (April 2017). The taxonomic identity of the plant was confirmed by the botanist of the Science and Research Branch, Islamic Azad University, Tehran, Iran. A voucher specimen of the plant has been deposited at the Herbarium of Islamic Azad University (voucher No. 11704). The ground seeds of *Cicer arietinum* were boiled in ten times tab water for 30 minutes and filtered by mesh (size no. 80) while it was warm, then the filtrate was spray dried in a ZPG Crude Drug Equipment model spray dryer (China). To obtain a fine dry extract, the following process parameters was used: inlet air temperature 174°C, outlet air temperature 102°C and pressure 400 psi. Capsules were filled by 330 mg spray dried extract of *C. arietinum* seeds, which was equal to 20 g of plant seed. Placebo was prepared by the same capsules including white wheat flour and looked the same as the chickpea capsules.

Total phenolics content

The total phenolics content was determined by spectrophotometry, using gallic acid as the standard, according the method described by Singleton and Rossi [23]. Briefly, 0.2 mL of the diluted sample extract of chickpea seeds was transferred in tubes containing 1.0 mL of a 1:10 dilution of Folin-Ciocalteu's reagent in water. Sodium carbonate solution (0.8 mL, 7.5% w/v) was added to the sample after 10 min. The tubes were then allowed to stand at room temperature for 20 min before the absorbance was measured at 750 nm. The total phenolic content was expressed as gallic acid equivalents in mg/g of seeds.

Study design

The sample size was calculated based on the formula for comparing the frequency of the stone dissolution between two groups. Considering a statistical power of 80% and type I error of 5%, effect size of 0.8 based on the results of a pilot study and drop out of 20%, forty one subjects were enrolled per group.

Block randomization method was used to randomize the participants in a 1:1 ratio, to receive either *C. arietinum* or placebo. Allocation was concealed using sequentially numbered, sealed, and opaque envelopes. The patients, the physician who prescribed the medications and assessed the patients, and the statistician were blind to the assignments throughout the study. Randomization, allocation, and interviewing

were carried out by separate persons. Per protocol analysis was conducted using the Statistical Package for Social Sciences (SPSS software, V. 16.0) (SPSS Inc., Chicago, IL, USA). Mean (± standard deviation) or number (and percentage) were used to describe the variables. Independent t-test was used for comparisons of variables between groups and paired t-test was done for within group comparisons. The p-value less than 0.05 was considered as significant.

Trial organization and study population

This randomized, double blind and placebo controlled clinical trial was conducted in the Tolooe Private Outpatient Urology Clinic in Hamedan, Iran, during July to September 2017. Overall coordination of the trial was from the Institute of Medicinal Plants, School of Persian Medicine, Iran University of Medical Sciences, Tehran, Iran. (Registration number: IRCT2017042433623N1).

Eligible participants in the study were male and female outpatients older than 18 years, which were diagnosed radiopaque renal stone by kidney-ureter-bladder x-ray and ultrasonography of the kidney, recently. Additional non-contrast spiral CT scan were done if needed. Patients with renal stones between 6 to 10 mm in the upper, middle and lower pole or the pelvis of each kidney without any complication that could be taken under observation none surgically by expert urologist were included in the study. Exclusion criteria were urinary tract infection, fever, marked hydronephrosis, acute or chronic renal failure, hepatic failure, diabetes, peptic ulcer, pregnancy, lactation or patient desire to immediate intervention for stone. All patients were treated on an outpatient basis. In addition, all subjects were instructed to drink 2 L water daily and perform their usual everyday activities. There were no dietary restrictions; however, patients were advised not to have an oxalate and/or calcium high rich diet. The home treatment period lasted 30 days or until stone dissolution. Use of any other chemical or herbal drugs to treat renal stone was prohibited. Patients were just allowed to use, as-needed, oral Tolmetin to the maximum dose of 1800 mg/day for pain relief. Size of stones were measured by ultrasonography.

Intervention and outcomes

The participants randomly received one *C. arietinum* capsule (330 mg) or placebo three times a day for 30 days. The primary outcome was dissolution of stone, from baseline to 30th day which was evaluated by ultrasonography. Secondary outcome parameters included changes in participants' plasma calcium, 24-h urine volume and 24-h urine calcium and magnesium concentrations.

Safety evaluation

Complete physical examinations were conducted at baseline, 14th and 30th day by an urologist.

All adverse signs and symptoms were recorded at each visit using a side-effect checklist. Blood biochemical parameters containing blood urea nitrogen (BUN), creatinine (Cr) for assessment of renal function; alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP) for assessment of hepatic function were carried out for all participants at the entry and the end of 30th day.

Results and Discussion

A total of 121 patients were screened for the study and 82 were randomized to trial medications. No significant differences were identified between groups at baseline (table 1). Seventy four patients completed the trial (38 in *C. arietinum* and 36 in placebo group) (figure 1). Although the number of dropouts in the placebo group was higher than that the treatment group, the difference was not statistically significant (p=0.09).

The stone size and biochemical parameters in participants were statistically identical at baseline as shown in table 1.

Table 1. Baseline characteristics of study subjects

Parameter	Intervention group Mean ± SD	Placebo group Mean ± SD	p value
Age (year)	44.55±7.31	44.50±6.99	0.97
Stone Size (mm)	7.15±1.34	7.08±1.09	0.80
BUN (mg/dL)	19.23±2.74	19.11±3.54	0.86
Cr (mg/dL)	1.04±0.19	1.07±0.20	0.54
ALT (U/L)	22.05±4.54	21.08±3.51	0.31
AST (U/L)	19.63±2.99	19.77±2.60	0.82
ALP (U/L)	130.76±13.32	128.14±12.51	0.38
Blood Calcium (mg/dL)	9.38±0.59	9.54±0.61	0.28
24 h Urine calcium (mg/dL)	125.18±11.69	127.03±13.91	0.53
24 h Urine magnesium (mg/dL)	93.02±10.71	90.30±10.03	0.26
24 h Urine volume (L)	1.67±0.16	1.70±0.12	0.41
Gender	M: 25, F: 13	M: 22, F: 14	-

BUN: blood urea nitrogen; Cr: creatinine; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; Ca: calcium; Mg: magnesium; M: male; F: female

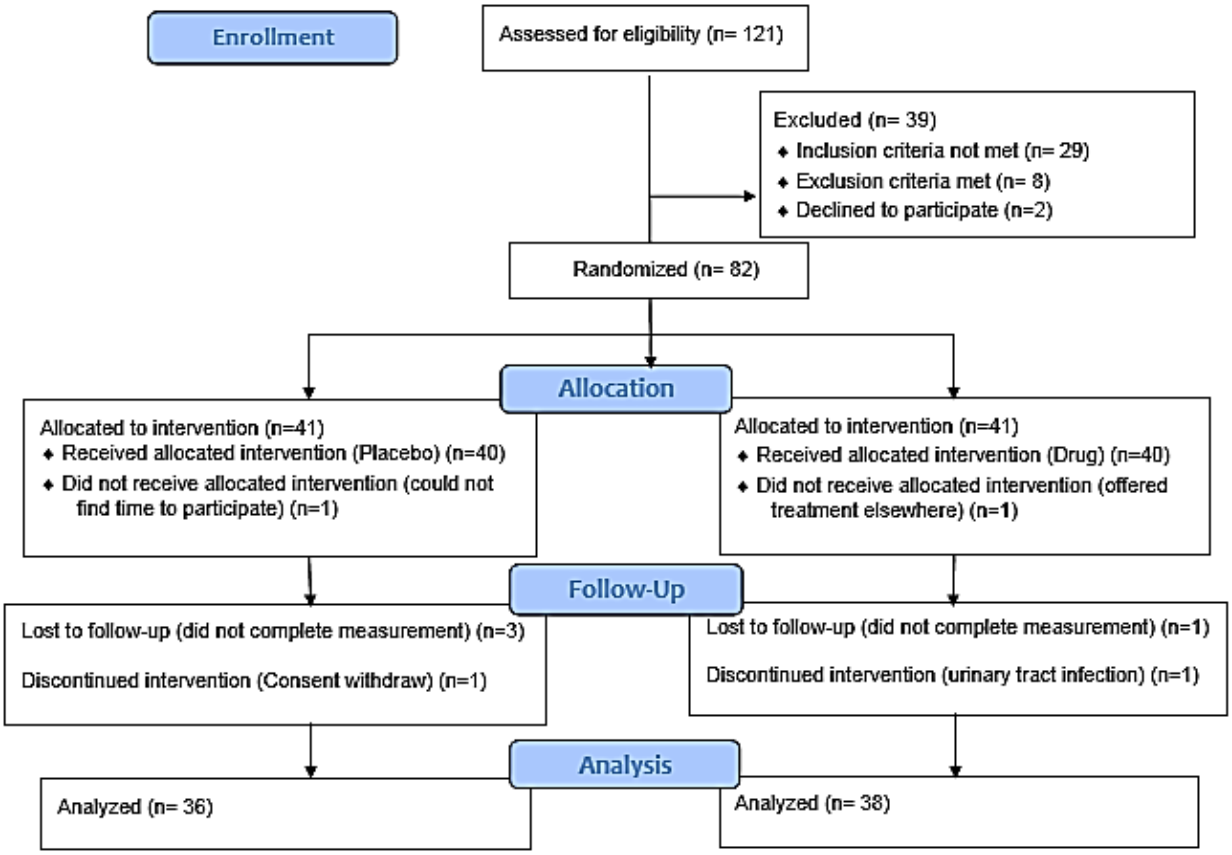

Figure 1. Study flow chart

After 30 days of intervention, in 38 patients of the *C. arietinum* group complete stone dissolution occurred in 9 (23.7%) patients and reduction in stone size was observed in 17 (44.7%) patients. On the opposite side, in total 36 patients of the placebo group, no response to treatment was observed. Comparing the tested groups, the changes of the stone size was significantly higher in the *C. arietinum* group ($p<0.001$).

The mean stone size at the base line of the study was 7.15 ± 1.34 mm which was reduced to 4.28 ± 3.09 mm ($p<0.001$) at the end of the treatment in patients treated with *C. arietinum*, while in the placebo group the mean stone size increased from 7.08 ± 1.09 mm to 7.15 ± 1.09 mm ($p=0.12$) (table 2).

There were no reports of serious pain in both groups during and after the end of the study. No adverse effects were either reported or observed during the entire study period.

Table 2 has summarized the data from several related para clinical, blood and urinary biochemical parameters measured to evaluate the efficacy, probable mechanisms of action and safety of *C. arietinum*. Blood levels of BUN and Cr were measured to evaluate *C. arietinum* safety on kidney. No significant difference in BUN and Cr blood was found between two groups after treatment ($p=0.79$ and $p=0.56$, respectively). Blood concentrations of ALT, AST and ALP were measured to evaluate the potential hepatotoxicity of *C. arietinum*. No significant difference in ALT, AST and ALP was found between two groups after treatment ($p=0.67$, $p=0.44$ and $p=0.23$, respectively). There was no significant difference in the blood calcium level between two groups after treatment ($p= 0.13$). Similarly, there was no significant difference in the calcium concentration of urine collected in 24 h between *C. arietinum* and placebo groups after treatment ($p=0.53$).

Comparing the groups, the changes of the urinary magnesium and the urinary volume were significantly higher in the *C. arietinum* group ($p=0.02$ and $p=0.04$, respectively) at the end of the treatment.

Table 2. The stone size and biochemical parameters at baseline and post treatment in each group

Variable	Group	Baseline Mean(±SD)	After 30 days Mean(±SD)	P value of paired t-test
Stone Size (mm)	Intervention	7.15(1.34)	4.28(3.09)*	<0.001
	Placebo	7.08(1.09)	7.15(1.09)	0.12
P value of t-test		0.80	<0.001	
BUN (mg/dL)	Intervention	19.23(2.74)	19.52(2.88)	0.52
	Placebo	19.11(3.54)	19.33(3.40)	0.57
P value of t-test		0.86	0.79	
Cr (mg/dL)	Intervention	1.04(0.19)	1.03(0.19)	0.64
	Placebo	1.07(0.20)	1.06(0.19)	0.10
P value of t-test		0.54	0.56	
ALT (U/L)	Intervention	22.05(4.54)	21.65(3.99)	0.58
	Placebo	21.08(3.51)	21.27(3.65)	0.75
P value of t-test		0.31	0.67	
AST (U/L)	Intervention	19.63(2.99)	19.84(3.10)	0.75
	Placebo	19.77(2.60)	20.38(2.99)	0.33
P value of t-test		0.82	0.44	
ALP (U/L)	Intervention	130.76(13.32)	129.45(10.38)	0.40
	Placebo	128.14(12.51)	126.61(9.85)	0.31
P value of t-test		0.38	0.23	
Ca Blood (mg/dL)	Intervention	9.38(0.59)	9.40(0.51)	0.82
	Placebo	9.54(0.61)	9.59(0.55)	0.45
P value of t-test		0.28	0.13	
24 h Urine Ca (mg/dL)	Intervention	125.18(11.69)	126.32(9.95)	0.48
	Placebo	127.03(13.91)	127.92(12.09)	0.59
P value of t-test		0.53	0.53	
24 h Urine Mg (mg/dL)	Intervention	93.02(10.71)	95.84(11.30)*	<0.001
	Placebo	90.30(10.03)	90.08(10.12)	0.33
***P* value of t-test**		0.26	0.02	
24 h Urine Volume (L)	Intervention	1.67(0.16)	1.76(0.12)*	<0.001
	Placebo	1.70(0.12)	1.70(0.12)	0.72
P value of t-test		0.41	0.04	

BUN: blood urea nitrogen; Cr: creatinine; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; Ca: calcium; Mg: magnesium; *****: statistically significant; placebo group n=36; intervention group n=38

Total phenolics content in seeds extract was determined by spectrophotometry according to the Folin-Ciocalteu colorimetric method [23] using gallic acid as the standard. The value obtained for total phenolics content of seeds was 0.46 mg/g extract.

In the present study, *C. arietinum* was evaluated for its safety and efficacy in patients with the size between 6 to 10 mm kidney stone. The main overall finding of this study revealed that *C. arietinum* had significant benefits over placebo in complete dissolving or reducing the size of stones in patients with 6-10 mm nephrolithiasis after 30 days of treatment with no side effects. To the best of our knowledge, the present study is the first randomized placebo-controlled trial on the effects of *C. arietinum* in nephrolithiasis, so it is not possible to make comparisons with others trials. The result of the present study confirmed the anti-nephrolithiatic effect for seeds extract of *C. arietinum* which was previously shown in an animal model [21].

The phytochemical analysis of *C. arietinum* seeds have shown the presence of carbohydrates, proteins amino acids and fixed oils. Moreover, it contains phytosterols, tocopherol, alkaloids, phenolic compounds and tannins, flavonoids, glycosides, saponins, magnesium, etc. Further, seed coat of *C. arietinum* is a good source of peptides with angiotensin-1 converting enzyme inhibitory activity [13-18].

Diuretic activity of *C. arietinum* may be due to active phytoconstituents such as alkaloids, steroids, tannins, phenolic compound, terpenoids and flavonoids [24,25], which are present in the seeds detected by phytochemical analysis [16,18]. These phytoconstituents can cause diuresis by increasing the urinary volume that decreases super saturation process, which is one of the favorable requisition factors for stone formation by crystallization.

Significant increase in urinary magnesium shows that magnesium as a microonutrient presents richly in *C. arietinum* [16,18], can bind with oxalate and form soluble complexes. Consequently, it reduces the super saturation of

calcium oxalate and decreases the growth and nucleation rates of calcium oxalate crystals. Numerous in vitro studies have confirmed that magnesium is a potent inhibitor of crystallization of calcium oxalate [2,24].

The oxalate precipitates in the urine as calcium oxalate due to its poor solubility. Calcium oxalate crystals and high oxalate levels in nephrons damage epithelial cells, inducing heterogeneous crystal nucleation and causing aggregation of crystals. Activity of antioxidant enzymes is decreased and lipid peroxidation is increased in the patients with kidney stones [24]. The development of tissue injury may depend on the balance between the generation of reactive oxygen species generation and the tissue antioxidant defense mechanism. Decreased tissue antioxidant enzymes can be followed to elevate free radicals in the stages of nephrolithiasis and it may be an oxidative stress for the renal tissue. Thus, it is suggested that the antioxidants can reduce the chance of deposition and excretion of small particles of calcium oxalate retained in the urinary tract [24,25]. Treatment with *C. arietinum* which contains considerable antioxidant phytoconstituents [16,18] can protect against oxidative stress induced tissue damage by increasing the activity of antioxidant enzymes and the level of glutathione. Consequently, it can be considered as a protective agent for nephrolithiasis.

Studies have shown that the Desi type seeds of *C. arietinum* which is applied in this study, contain up to 13-, 11-, and 31-fold more total polyphenol content (TPC), total flavonoid content (TFC), and antioxidant activity, respectively, than the other type (the Kabuli) seeds [13]. Thus, *C. arietinum*, especially the Desi type might contribute significantly to the management and/or prevention of degenerative diseases associated with free radical damage such as nephrolithiasis due to their high antioxidant activity.

Saponin derivatives have appeared as components of the *C. arietinum* which are claimed to have anti-urolithiatic property [16,24] could be considered as another reason for effectiveness of the herb in urolithiasis.

In addition to antioxidant activity, phytosterols of *C. arietinum* have anti-inflammatory and antioxidant properties [16,24,26] which can be effective in management of urolithiasis. Tannins, flavonoids, and isoflavonoids which are found richly in *C. arietinum*, can lead to relaxation of smooth muscle of the urinary tract which could facilitate the expulsion of stones from the kidney and diminished the size of calculi, as it has been reported in rats [16,18,25]. The phytochemical analysis of *C. arietinum* has revealed the presence of peptides with angiotensin I converting enzyme inhibition activity in the seed coat [16]. Renin-angiotensin system activates the nicotinamide adenine dinucleotide phosphate hydrogen (NADPH) oxidase in kidney cells, which produces reactive oxygen species (ROS) followed by renal cell injury and inflammation. This loss of membrane integrity, provokes fibrosis and collagen formation, facilitates calcium oxalate retention and subsequent calculi formation. The inhibition of angiotensin converting enzyme significantly reduces calcium oxalate crystal deposition and renal inflammation by inhibition of NADPH oxidase and consequently decrease in ROS in renal cells [27].

It has been shown that vitamin E administration can prevent crystal precipitation in the rat kidney. Vitamin E has also been shown to decrease the urinary excretion of calcium, oxalate and restore the antioxidant ability in the blood of patients who underwent surgical nephrolithiasis removal [16,18,28]. Therefore, the presence of tocopherol as a natural form of vitamin E which has found in seeds of *C. arietinum*, can be considered as one of the potential mechanisms responsible for the anti-nephrolithic effect of the seeds.

The significant benefits in reduction of stone size by using *C. arietinum* without side effects, may confirm the application of the seeds as an alternative treatment for nephrolithiasis in Persian traditional medicine.

Medicinal plants exert their effectiveness at different stages of stone pathophysiology with multidimensional pharmacological actions such as diuretic, litholytic, lithotriptic, antioxidant, angiotensin converting enzyme inhibitory, anti-inflammatory, analgesic, antispasmodic, making balancing between inhibitors and promoters of crystallization, changing the ions concentrations in urine, etc [27]. This study showed that *C. arietinum* extract is an effective and safe drug in a short-term treatment of calcium renal stones. This effect may be due to its multidimensional pharmacological actions. The study supports the traditional information regarding the antiurolithiatic activity of *C. arietinum*. Based on these results, a therapeutic role of *C. arietinum* is suggested for patients with calcium renal stone

size less than 10 mm, which is an accessible and cost-effective therapy with no side effects. Obviously, further detailed studies aimed at discovering the mechanism of action of *C. arietinum* and clinical studies involving a larger population of patients and longer period of follow up will be necessary to fully explain and confirm the results obtained in the present study.

Acknowledgments

This study is based on Ph.D thesis of Mahdi Biglarkhani, which was supported by the School of Persian Medicine, Iran University of Medical Sciences, Tehran, Iran. We would like to thank Dr. Iraj Mehregan for identification of the plant as *Cicer arietinum*.

Author contributions

Mahdi Biglarkhani has made substantial contribution in designing, acquisition of data and drafting the manuscript; Omid Sadeghpour was the principal investigator and involved in the preparation of product; Mohammad Ali Amir Zargar was the investigator, the clinical coordinator and participated in the design and revision of the manuscript; Fataneh Hashem-Dabaghian was one of the thesis's supervisors, developed the theory and critically revised the manuscript and participated in the data analysis and interpretation; Farshad Amini Behbahani was one of the thesis's supervisors, developed the theory and critically revised the manuscript; Azam Meyari contributed to the collection of data and was involved in design and revision of the manuscript.

Declaration of interest

The authors declare that there is no conflict of interest. The authors alone are responsible for the content of the paper.

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Abbreviations

ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BUN: blood urea nitrogen; *C. arietinum*: *Cicer arietinum*; Ca: calcium; Cr: creatinine; F: female; M: male; Mg: magnesium; ROS: reactive oxygen species; TFC: total flavonoid content; TPC: total polyphenol content; NADPH: nicotinamide adenine dinucleotide phosphate hydrogen