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Clinical trial

Effect of topical chickpea oil (*Cicer arietinum* L.) on knee osteoarthritis: A randomized double-blind controlled clinical trial

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ABSTRACT

Introduction: Chickpea oil (*Cicer arietinum* L.) is considered to have anti-inflammatory properties and is of therapeutic importance. It has been used topically in Persian medicine and compared other treatments and it is easily available and low cost. In clinical practice patients applying chickpea oil have expressed their satisfaction. Given the lack of valid scientific studies, this randomised controlled trial was conducted to evaluate the effect of topical chickpea oil on knees affected by osteoarthritis.

Methods: Patients (n = 75) referred to the rheumatology clinic with a diagnosis of osteoarthritis of the knee were randomly assigned into three groups; chickpea oil, piroxicam gel or paraffin and were treated for three months. Patients self-medicated massaging the oil into the affected knee twice a day for three months. Physical activity, stiffness and pain were measured at baseline and at the end of 3th month. The groups were compared at the end of treatment.

Results: WOMAC scores showed significant reduction in pain, stiffness, and difficulty in activity in the chickpea oil group compared with the piroxicam or paraffin group ($p < 0.05$). VAS mean pain scores were 5.42 for the placebo group, compared wih 3.92 for the piroxicam group and 3.88 the chickpea oil group, which was significantly different ($P < 0.001$). No adverse effects were reported by patients.

Conclusions: The results of this study demonstrated that chickpea oil could be effective in relieving pain, reducing motion stiffness, and increasing activity in osteoarthritis patients.

1. Introduction

Osteoarthritis (OA), also known as degenerative arthritis, is a progressive joint disease that affects joint cartilage, the synovial membrane, subchondral bone, and the surrounding tendons and ligaments [1–3]. Some of the strongest and well-established risk factors of OA include; old age, female gender, congenital joint malformation, prior knee injury, and family history [4].

Since there is no definitive treatment [5] for this disease, one of the main goals of the treatment is to reduce the symptoms of osteoarthritis. Treatments include non-pharmacological treatments (e.g. patient education, exercising, weight control, physical therapy, physiotherapy) and drug therapies (e.g. administration of non-steroid anti-inflammatory drugs, local anesthetics, intra-articular injection of glucocorticoids, and hyaluronic acid) [6]. Nonsteroidal anti-inflammatory medicine contains some adverse effects (e.g. digestive, cardiovascular, renal, hematopoietic, and liver complications). Therefore, it is suggested to reduce the effective dose and duration of consumption with topical use of these drugs which is achievable with traditional therapies [7].

Traditional Medicines (TM) are the oldest form of health care in the world and used for prevention and treatment of physical and mental illnesses. Different societies historically developed various useful healing methods to combat a variety of health-threatening and life-threatening diseases. TM is also known as complementary and

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alternative, or ethnic medicine which is still plays a key role in many countries [2]. Traditional medicines are quite popular among the general public, especially patients suffering from chronic diseases, however in most cases the efficacy and safety require further validation. These patients tend to use traditional medicine because it is accessible, inexpensive, and natural. Besides, modern medicine encounters several difficulties in the treatment of osteoarthritis [1]. Among various traditional systems of medicine, Persian Medicine (PM) is among the oldest and most valuable ones. PM history dates back to thousands of years ago. It flourished with the efforts of Persian Muslim physicians like Rhazes (865–925CE), Haly Abbas (949–982CE), Akhawayni (?–983CE), Avicenna (980–1037CE), Jorjani (1042–1137), and many others in early medieval periods [8].

Oils are widely used in PM and over 50 types of medicinal oils have been made out of 31 plants and their various parts i.e. flowers, leaves, and fruits. Medicinal oils have been traditionally used via topical, oral, and even nasal routes to the target particular areas of the body to fight specific ailments. Topical forms are most often used for nervous, musculoskeletal and skin conditions [9].

As far as osteoarthritis is concerned, chickpea oil has been recommended in PM to treat joint pains. The anti-inflammatory effects of chickpea have been shown in some studies [10,11]. *Cicer arietinum* (Fabaceae) is one of the most popular legumes in most parts of the world [2]. It is used for the treatment of many diseases (e.g. diabetes, hypocholesterolemia, diarrhea, coagulation diseases, cancer, nephrolithiasis, cutaneous disorders, and cosmetics) [12,13].

Chickpea (Nokhod in Persian) grows in Iran, Australia, Mexico, Myanmar, Tanzania, Turkey, etc. It is a source of protein and carbohydrates containing some mineral elements (e.g. calcium, magnesium, iron, and phosphorus), vitamins (e.g. thiamine and niacin) and unsaturated fatty acids (e.g. oleic acid and linoleic acid) [13]. Chickpea is considered to have anti-inflammatory properties [14].

The documented effects of the use of chickpea suggested that this should be further investigated. A randomized controlled trial was designed to assess the efficacy and safety of topical chickpea oil on knee osteoarthritis.

1.1. Study design

The study was designed as a three armed double-blind, randomized, placebo-controlled clinical trial using a parallel design. The study had three parallel intervention arms; the trial medication (chickpea oil), piroxicam (a topical non-steroidal medicine), and placebo (paraffin).

1.2. Ethical approval

The study protocol was approved by the Local Medical Ethics Committee of Rafsanjan University of Medical Sciences with reference number: IR.RUMS.REC.1397.092 and the study was conducted according to the principles of the Declaration of Helsinki. The trial protocol was registered in the Iranian Registry of Clinical Trials database under registration IRCT20181030041500N1.

All enrolled participants returned their signed informed consent forms if they wished to participate and their information was kept confidential. The medication used for the participants in this study were given out free of cost. The patients willingly chose whether they desired to remain in the study or to be excluded.

1.3. Inclusion and exclusion criteria

Between March and September 2018, all patients referred to the rheumatology clinic of Rafsanjan, (an academic center affiliated with RMU) were considered for the trial if they met the following inclusion criteria; between 50 and 70 years old, diagnosed with knee osteoarthritis (based on the American College of Rheumatology criteria) and approved by a rheumatologist and experiencing knee pain in the last 24 h. Average knee pain within 24 h was based on the linear Visual Pain Scale (VAS) of 4–7 cm [15].

Patients were excluded if they had any serious co-morbidities (e.g. liver disorders, renal failure, history of peptic ulcer disease, dermatologic disorders affecting the surrounding skin of the knees) patients with inflammatory diseases (e.g. lupus, rheumatoid arthritis, history of brucellosis, etc.), any oral corticosteroid intake over the last four weeks, any corticosteroid injections over the past six months, currently having a fever, consuming medicinal plants, chickpea allergy, unwilling to continue participating in the study, failure to observe the study protocol, any complications caused by chickpea oil, consuming food and medical supplements, and daily analgesic consumption. Patients meeting the above inclusion and exclusion criteria were asked to participate in the study.

1.4. Preparation of test drug, placebo and standard drug

The chickpeas were purchased from a local market in Kerman, Iran. The plant species were identified by an herbalist and a voucher sample (No. KF-1508) was kept in the Faculty of Pharmacy in Kerman.

The chickpea oil was prepared according to the methodology of PM called Qarabadin (Pharmacopeia) [16]. To this end, 50 g of chickpea powder was soaked in 300 mL of distilled water overnight and then it was boiled for one hour. Afterwards, it was filtered using a Buchner funnel vacuum and the chickpea extract got mixed with an equal amount of sesame oil (Ardakan sesame oil). The extract was heated again for a complete evaporation of aqueous extract, so that only oil would remain. The chickpea oil was poured into 30 ml dark bottles. The pharmaceutical graded paraffin was used as a placebo which has been packed in the same containers of darkened color and it was odorless which supported the blinding of the design. Piroxicam gel 0.5 % (Najo) is a topical nonsteroidal medicine is used to treat pain or inflammation caused by osteoarthritis or rheumatoid arthritis [17]. Piroxicam was supplied as the positive control medication and was prescribed for the third arm of the study. We selected the piroxicam gel because it was the most similar in terms of topical application.

1.5. Interventions

At the beginning of the study, a demographic questionnaire including age, sex, marital status, educational level, and employment status was completed by the participants. Weight of the subjects was measured to a digital weighing accuracy of 0.1 kg at the beginning of the study and their height was measured with an accuracy of 0.5 cm without shoes and with the minimum coverage and the body mass index (BMI) was also calculated [18]. Clinical examinations and confirmation of disease were performed by rheumatology specialist in the Rheumatology clinic of Rafsanjan. All stages namely the interview, questionnaire, and anthropometric measurements were performed by a qualified expert who was unaware of the group allocations.

The patients were assigned to three groups, viz. A: piroxicam gel, B: chickpea oil and C: paraffin use twice a day for three months. All the participants were allowed to use acetaminophen tablets (500 mg) as a painkiller during the trial period. Before the study was carried out, the medications were double-blinded through coding as A, B, and C in the same packages by someone other than the researcher. The medications were prescribed as either A, B or C by the rheumatologist and were delivered by another person. They were prescribed twice a day for three months. Patients were instructed to use the medications on their knees and surrounding areas (i.e. 2 cc chickpea oil and paraffin, and a pea size diclofenac gel). It's worth noting that the patients were advised not to massage the mentioned zone. Moreover, the participants didn't have to apply the medications on the skin for a certain period of time as long as the mentioned areas were completely smeared with the medications. Patients were followed up to get checked for potential side effects and adherence to the study protocol by referring to the clinic and also by

making calls every week. If more than 90 % of the package content was consumed, full adherence of the individual could be determined by examining the content of the packages during the first month. Meanwhile, the data analyst was not aware of the intervention used by the patients.

1.6. Outcome measures

The patients were evaluated by the Visual Analogue Scale (VAS) as a 10 cm ruler by which the patient is asked to show her/his pain intensity from zero to 10 (0-3: mild pain, 4-7: moderate pain, and 8-10: severe pain). Patients were asked to mark their pain intensities on the ruler before and after taking the medication at the end of the third month.

Response to the treatment was considered to reduce pain by more than 1.5 cm.The patients' performance was evaluated by the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) [19] as a self-administered and validated tool including 24 questions in which five questions were dedicated to the pain; pain score ranged from 0 (no pain) to 4 (extreme pain);

14 questions were on physical activity; ranging from 0 (no difficulty) to 4 (the most severe difficulty); and two questions were on joint stiffness ranged 0 (no stiffness) to 4 (the worst stiffness). Five numbers, from 0 to 4, were taken into consideration for each option. Nothing was changed in the trial outcomes after the trial started. Changes were measured only at the end of the three-month period and were compared with the baseline.

1.7. Randomization and blinding

Of 140 patients assessed for eligibility, 79 patients were eligibile and randomly allocated to three parallel groups; the chickpea oil drug, piroxicam gel and paraffin groups groups by the secretary of the clinic who had been trained and instructed to use a block-randomization list. The list was generated by a computer as a non-stratified list with the same block lengths. In order to double-blind the study, the drugs were put in identical packages coded as A, B, and C by a person other than the researcher. The rheumatologist prescribed the drug as A, B or C medication and the drug was delivered by another person. Clinical symptoms were assessed by a rheumatologist who was not aware of the type of medication used by each individual. The physicians, researchers and statisticians were blinded to the allocation of patients.

1.8. Sample size

After investigating previous studies, [20] the sample size was calculated by considering a confidence interval of 95 % and a power of 80 %. it was determined to be 25 participants in each group.

1.9. Statistical analysis

The demographic and clinical characteristics of included patients are shown as the mean ± standard deviation (SD) for continuous variables.

Data were analyzed using SPSS software V. 19. The Kolmogrov-Smirnov test was used to determine the distribution of data. Mean values of quantitative data between the groups were compared by one-way ANOVA and Mean values of quantitative data within the groups before and after the intervention were compared by Paired *t*-test. Fisher's exact test was applied to compare the frequency distribution, pain status, and response to the intervention. The Chi-square was applied to compare qualitative variables.

2. Results

Between March 2018 to September 2018 140 patients met the inclusion criteria for the study, 61 failed to meet the criteria and 4 declined to participate leaving 75 people who were finally recruited (Fig. 1).

The baseline properties of the patients are presented in Table 1 (age, sex, weight, and duration of activity). On entry, there were no significant differences between the three arms of the study in terms of demographic and clinical parameters (P value >0.05).

Outcome measures were assessed at the end of the study at 3 months after continuous application as initially instructed. According to the VAS, the mean score of pain at baseline for the placebo, chickpea, and piroxicam group was 5.58, 5.94 and 5.80, respectively and there was no significant difference between the groups ($P > 0.05$). The mean score after the intervention was 5.42 for the placebo group, 3.88 for the chickpea oil group and 3.92 for the piroxicam group which was significantly different between the groups ($P = 0.001$) (Table 2).

Pain, stiffness, and activity scores measured by WOMAC are reported in Table 3. The difference in these three parameters between groups at baseline before the intervention was not significant ($P > 0.05$). Pain, stiffness and physical function scores after intervention in chickpea oil group and piroxicam group significantly decreased compared with the placebo group($P < 0.001$). The differences of activity scores before the intervention were significant ($P < 0.05$), so the researchers had to use covariant analysis (Table 3).

2.1. Safety and tolerability

Chickpea oil was well received by patients, resulting in no adverse effects and susceptibility neither local nor systemic. No adverse effects were observed in paraffin and diclofenac groups.

3. Discussion

In the present clinical trial study, the efficacy of chickpea oil in the treatment of pain and clinical symptoms of knee osteoarthritis was examined in a double-blind randomized clinical trial. Chickpea oil had a significant effect on the pain relief and the symptoms of knee osteoarthritis compared to the placebo group. This study also revealed that physical activity and stiffness were improved in patients receiving chickpea oil compared to the placebo group.

A total number of 75 OA patients; consisting of 9 men and 66 women participated in this clinical trial. As in other studies [21], the prevalence of OA was higher among women comparing to men. This study manifested that chickpea oil, as a traditional topical formulation, could relieve the pain of OA patients, reduce stiffness, and improve physical function. Comparing the groups; the analysis showed that there was a more significant improvement in all the results over the study period in the chickpea oil group compared to the placebo group ($P < 0.05$).

Osteoarthritis is recently considered an inflammatory condition similar to arthritis and based on our knowledge obtained from accessible published data; the use of topical chickpea oil for treating this disease has not been studied yet. anti-inflammatory and analgesic properties of chickpea have been investigated in previous studies [22,10]. Chickpeas contain several phenolic compounds [23] which are attributed to be responsible for the anti-inflammatory effects of the chickpea oil. Khazaeli et al.(2019) reported that luteolin (flavonoid) is present in henna oil which is a Persian medicinal product. Hence, phenolic compounds may also be abundant in chickpea oil [24].

Studies conducted on the oily content of chickpeas and extracts from which they were produced reveal that chickpeas contain antioxidant and anti-inflammatory substances. 3.8–10 % of the content of chickpea is fixed oil. However, chickpea fixed oil contains tocopherols, sterols, and tocotrienols that are nutritionally and therapeutically important. Cholesterol alpha tocopherol is higher compared to other legumes such as lentils, green beans, red beans and mung bean. Alpha-tocopherols have antioxidant and anti-inflammatory properties [11,25].

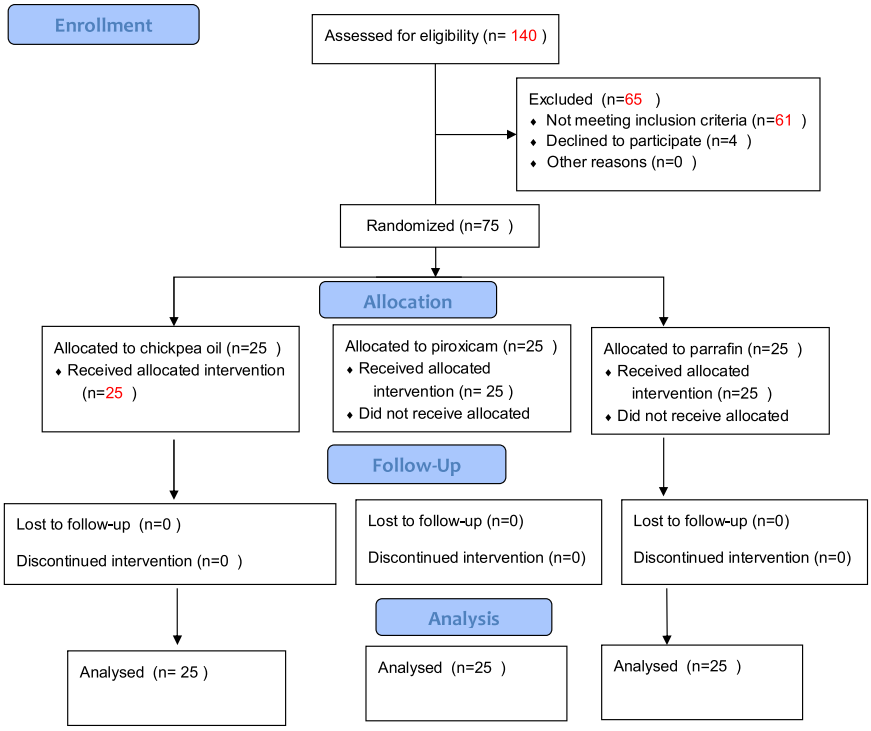

Fig. 1. Flowchart of the inclusion, allocation and outcomes of the trial.

Table 1
Baseline characteristics of patients.

	Chickpea oil	Piroxicam	Paraffin	P_value
Age (years)	59.36 ± 9.03	56.4 ± 6.58	55.92 ± 6.60	0.22
Male/Female	5/20	2/23	2/23	0.486
Weight (kg)	70.6 ± 9.70	69.76 ± 9.25	68.4 ± 10.22	0.724
Activity (h/day)	4.28 ± 1.45	4.34 ± 1.24	4.34 ± 1.26	0.983
BMI	28.4 ± 4	28.45 ± 3.96	28.81 ± 3.21	0.907

BMI: Body Mass Index.

Table 2
Comparison of mean pain VAS scores before and after intervention.

	Pain scale Average		P_value [a]
	Before intervention	After intervention	
Chickpea oil	5.94 ± 0.63	3.88 ± 0.97	0.001
Piroxicam	5.80 ± 0.55	3.92 ± 0.67	0.001
Paraffin	5.58 ± 0.73	5.42 ± 0.77	0.116
P_value [b]	0.146	<0.001	—

P_value [a] is calculated by Paired *t*-test for within group comparison.
P_value [b] is calculated by one-way ANOVA for between group comparison.

The oil discussed in this study is a PM obtained by heating the aqueous extract of chickpea in the sesame oil. The analgesic effect of chickpea oil has been reported in Persian medicine sources [12,22]. Masroor et al. (2018)investigated the anti-inflammatory effect of methanolic and ethanolic extracts of chickpeas using the Carrageenan model. Both extracts showed the highest anti-inflammatory effect at the dosage of 500 mg/kg, which was attributed to the presence of phenols and flavonoids in the chickpeas. Given that the anti-inflammatory effect of chickpea extract has been reported in the Carrageenan model [26,27], it can be concluded that chickpea extract acts by inhibiting prostaglandin and histamine [26]. Phytochemical analysis of the extracts revealed the presence of flavonoids, tannins, and saponins in the methanolic and ethanolic extracts of chickpea [23].

Table 3
Comparison of mean WOMAC pain, stiffness, physical activity scores before and after intervention.

	Chickpea oil	Piroxicam	Paraffin	P_value [a]
Score of pain				
Before	10.88 ± 2.45	11.20 ± 2.19	9.68 ± 2.30	0.057
After	7.00 ± 2.08	6.88 ± 1.69	9.20 ± 2.08	< 0.001
P_value[b]	< 0.001	< 0.001	0.011	
Stiffness				
Before	2.60 ± 0.91	2.44 ± 0.86	2.76 ± 0.96	0.472
After	1.56 ± 0.58	1.48 ± 0.58	2.80 ± 1.11	< 0.001
P_value [b]	< 0.001	< 0.001	0.802	
Physical activity				
Before	38 ± 6.70	37.80 ± 7.15	31.92 ± 8.02	0.006
After	22.04 ± 5.61	22.80 ± 7.03	30.84 ± 5.66	< 0.001
P_value [b]	< 0.001	< 0.001	0.304	

WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.
P_value [a] is calculated by one-way ANOVA for between group comparison.
P_value [b] is calculated by Paired *t*-test for within group comparison.

Isoflavones of the chickpea have an effective role in the treatment of menopause symptoms, osteoporosis, heart diseases, and cancer prevention. Chickpea isoflavones can also have an anti-inflammatory effect [28].

In a study done by Shoara et al., the effect of chamomile oil, as a Persian traditional medicine product, was investigated on osteoarthritis and the analgesic effects of chamomile oil were reported. They also used the two scales of VAS and WOMAC, with patients being evaluated weekly and treated for three weeks. However, in this study, the patients received three months of medication and were evaluated before the treatment and at the end of three months [1].

Topical drugs have to pass through the skin first to create their effect. To increase the absorption of topical medicines into the skin, sometimes they need to be formulated with ingredients that can help with the absorption of one of these substances. One group of these substances are vegetable oils including sesame oil. In order to penetrate the skin, the drug needs to pass at least two paths, a polar path and a

non-polar path. The polar pathway is related to stratum corneum proteins and the non-polar pathway is related to its lipid composition. Sesame oil, with an average of 25 % protein and 67 % globulin, is able to pass the polar pathway of the skin quite well and pass the non-polar pathway through unsaturated fatty acid molecules. So, sesame oil can cause more absorption to the skin. In Persian traditional medicine sources, sesame oil is used as a base for the preparation of oils as well as in the production of chickpea oil. Therefore, the anti-inflammatory and analgesic compounds of chickpeas can penetrate the skin through sesame oil and exert their effects [29].

Many studies have been conducted on the antinociceptive effects of herbal compounds concerning osteoarthritis, including comfrey extract cream, capsicum gel, urtica dioica, a mixture of herbs called Marhame-Mafasel and Chinese herbs. Among these, Marhame-Mafasel like the present study is one of the traditional PM that has been able to improve three indices of pain, physical function and stiffness in patients with knee osteoarthritis compared to placebo [30].

In a review study conducted by Altman (2011), it was concluded that the use of NSAIDs in OA treatment was not significantly different from systemic therapy. However, since the complications of the systemic use of these drugs on patients are higher than those of topical use; topical use of medications is prevalent in the treatment of mild to moderate OA [31]. Given that there is no definitive treatment for this disease [32], one of the main goals of the treatment is to reduce the disease symptoms. The effects of chickpea oil and piroxicam were similar in this study with the difference that chickpea oil did not have steroid complications, so it could be a useful option to reduce the pain plus its lower costs for patients.

3.1. Limitations of the study

One of the limitations of this study is the lack of standardization of chickpea oil. As a result, the constituents and the amount of the chickpea oil used in this study were equivocal. Another limitation of this study was the inability to measure patients' recovery parameters at the end of each month. The parameters were measured and analyzed only three months after receiving the treatment. Chickpea oil may have had a therapeutic effect at the end of the first and second month, but it might have remained hidden. Lack of consistency in acetaminophen use is another limitation of this study.

4. Conclusion

The results of this study demonstrate that chickpea oil could be effective in relieving pain, reducing motion stiffness, and increasing activity in OA patients. Given that there were no significant relationships between chickpea oil and piroxicam groups, the former could be used as complementary medicine in the treatment of OA patients. It is recommended that for additional studies, standardized chickpea oil be used in a larger sample size and that patients' recovery parameters be evaluated at the end of each month.

Authors contributions

All authors contributed significantly to this article including the design of the clinical trial, the analysis and interpretation of data, and the drafting and revision of the article. All three authors approved the final version.

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Declaration of Competing interests

The authors declare no conflict of interests.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.eujim.2020.101076.

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