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The efficacy of topical sesame oil in patients with knee osteoarthritis: A randomized double-blinded active-controlled non-inferiority clinical trial

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ABSTRACT

Objective: Sesame oil is an herbal product that has been used to treat the joints pain in several traditional medicines. In this study, we evaluated the efficacy of topical sesame oil versus diclofenac gel in patients with knee osteoarthritis (OA).

Methods: One hundred and four patients were randomly enrolled in two arms of the trial. Patients were treated by topical sesame oil or diclofenac (three times a day) for 4 weeks. Outcome measures were knee pain via visual analogue scale (VAS), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) questionnaire, knee joint's flexion angle, 8-meter walk test and number of used analgesics. Patients were evaluated at baseline, 2 and then 4 weeks after the intervention.

Results: At the follow-up visits, sesame oil was not inferior to diclofenac regarding scores of WOMAC pain, 8-meter walk test, and knee flexion angle. Although, its non-inferiority was not proved regarding scores of VAS, WOMAC stiffness, and WOMAC total at the 4th week. Moreover, sesame oil was not inferior to diclofenac regarding consumed analgesics.

Conclusion: It seems that the topical sesame oil was non-inferior to diclofenac gel on the reduction of the knee OA pain and improvement of some indicators of its function.

1. Introduction

Osteoarthritis (OA) is the commonest type of arthritis among people in the world. The prevalence of this disease is high and unprecedented [1,2] Most patients present with joint pain and functional limitations. Therefore, OA is one of the most common causes of chronic disability, especially in the elderly.[3]

Non-pharmacologic management (such as weight loss and exercise), oral and topical medication or analgesics such as non-steroidal anti-inflammatory drugs (NSAIDs), intra-articular steroids, and finally surgery are several treatment modalities to help patients to relieve symptoms of the OA [4,5] Nevertheless, there are several side effects related to each of them. Thus, finding new therapeutic options for OA is necessary. Also, global increasing interest in the use of herbal remedies for treatment of chronic diseases motivated the researchers to design clinical studies on herbal remedies for OA.[6–9]

Sesamum indicum L. (family *Pedaliaceae*) is known as *Konjed* in Persian and sesame in common English. Sesame oil, as a widely used oil in the world, is a natural food stuff and herbal product derived from sesame seeds [10] It has been used to treat various diseases in traditional and complementary medicines, especially in traditional Persian medicine, for thousands of years.[11–13] Previous animal and clinical studies

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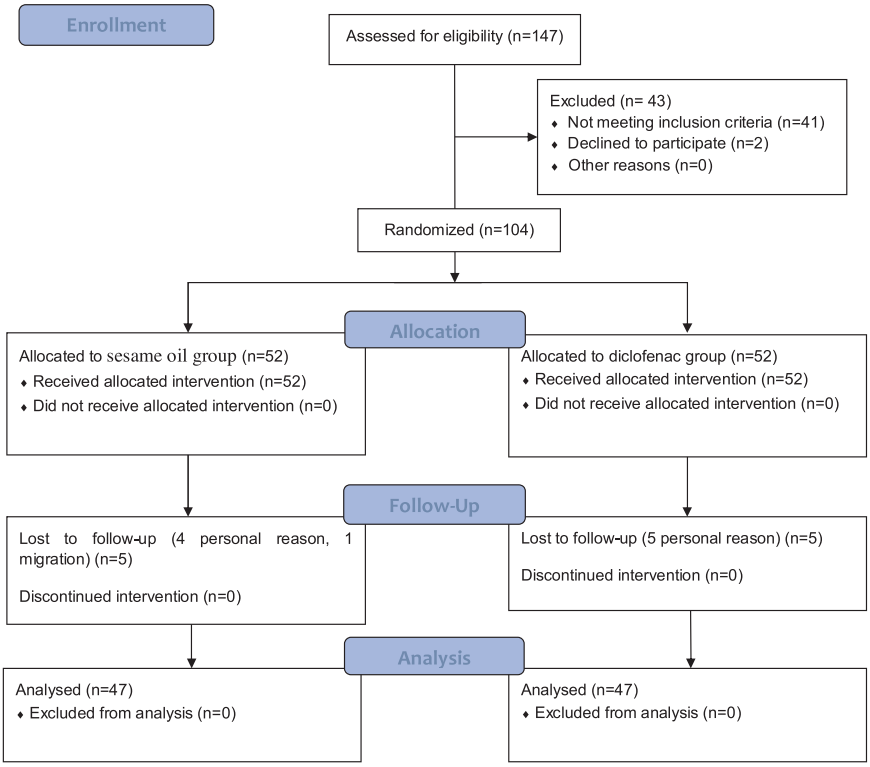

Fig. 1. CONSORT Flow diagram of the patients' screening, enrollment, allocation, follow-up, and analysis.

Table 1
Baseline demographic and clinical data of the patients in both groups of the study.

Demographic data	Sesame oil (n = 47)	Diclofenac gel (n = 47)	*p* value
Age (years), Mean ± SD	57.5 ± 12.5	57.5 ± 9.1	0.976
BMI* (Kg/m2), Mean ± SD	28.7 ± 3.8	27.8 ± 4.5	0.292
Duration of disease(Month), Mean ± SD	72.3 ± 62.7	87.0 ± 67.4	0.298
Male/female (n)	7/40	10/37	0.421
Active/Inactive** (n)	39/8	42/5	0.370

* Body mass index.
** Inactive: housekeeper, retired or unoccupied.

Table 2
Changes of outcome measures (mean ± SD) before and after the intervention.

		Sesame oil (n = 47)	Diclofenac gel (n = 47)	*P*-value[1]
Visual analogue scale (VAS)	Baseline	58.04 ± 10.93	59.09 ± 9.36	0.542
	2 weeks	50.36 ± 12.12	51.36 ± 11.33	0.690
	4 weeks	45.00 ± 12.78	44.43 ± 13.39	0.412
	P-value[a]	**< 0.001**	**< 0.001**	
	P-value[b]	**< 0.001**	**< 0.001**	
	P-value[c]	**< 0.001**	**< 0.001**	
Knee flexion angle	Baseline	104.94 ± 27.78	114.32 ± 21.37	0.079
	2 weeks	115.42 ± 22.87	113.18 ± 22.58	0.209
	4 weeks	120.83 ± 18.95	121.14 ± 14.51	0.102
	P-value[a]	0.314	0.942	
	P-value[b]	**< 0.001**	**0.019**	
	P-value[c]	0.053	**0.012**	
8-meter walk test	Baseline	11.73 ± 5.09	10.37 ± 2.06	0.104
	2 weeks	10.80 ± 3.79	10.60 ± 2.43	**0.011**
	4 weeks	11.07 ± 3.81	10.40 ± 2.53	0.422
	P-value[a]	**0.001**	0.379	
	P-value[b]	0.064	0.913	
	P-value[c]	0.243	0.266	
Number of analgesic consumption	2 weeks	19.16 ± 6.43	15.74 ± 7.93	**0.040**
	4 weeks	19.38 ± 6.96	21.45 ± 6.62	**0.022**
	P-value[c]	0.744	**0.002**	

P-value[1]: comparison between study groups; P-value[a]: comparison between baseline and 2 week; P-value[b]: comparison between baseline and 4 week; P-value[c]: comparison between 2 week and 4 week.

have shown the effectiveness of oral consumption of sesame oil in the treatment of OA.[14–18] Furthermore, sesamine as one of the major active ingredients of sesame was assessed for possibility of chondroprotective effects. Its efficacy was supported in an animal study of OA model.[19]

Therefore, we designed a randomized controlled clinical trial to evaluate the efficacy of the topical use of sesame oil versus diclofenac gel in patients with knee OA.

2. Material and methods

2.1. Trial design

The study was designed as a prospective randomized double arm, double-blind active-controlled clinical trial. We surveyed the effect of topical use of sesame oil compared to diclofenac sodium gel (%1) in patients with knee OA (allocation ratio 1:1) in this trial. No changes occurred to methods after the proposal was approved.

2.2. Compliance with ethical codes

The study framework was in compliance with the guidelines of Declaration of Helsinki (1989 revision) and IAHAIO Tokyo Declaration. Local Medical Ethics Committee of Fasa University of Medical Sciences (FUMS) approved this trial, as well (Approval number: IR.FUMS.REC.1394.39). A signed written informed consent form should be returned by subjects who planned to participate. Moreover, the study was registered by Iranian Registry of Clinical Trials with the code: IRCT2017081711341N8.

Table 3
Changes of WOMAC questionnaire scores before and after the intervention.

WOMAC		Sesame oil (n = 47)	Diclofenac gel (n = 47)	*P*-value[1]
Total	Baseline	39.87 ± 15.24	39.90 ± 17.34	0.991
	2 weeks	33.01 ± 15.68	32.78 ± 17.84	0.884
	4 weeks	29.78 ± 16.75	27.49 ± 15.95	0.334
	P-value[a]	**< 0.001**	**< 0.001**	
	P-value[b]	**< 0.001**	**< 0.001**	
	P-value[c]	**< 0.001**	**< 0.001**	
Pain	Baseline	8.35 ± 3.60	8.22 ± 4.11	
	2 weeks	6.60 ± 3.55	6.72 ± 4.14	0.902
	4 weeks	5.88 ± 3.90	5.49 ± 3.51	0.967
	P-value[a]	**< 0.001**	**< 0.001**	0.589
	P-value[b]	**< 0.001**	**< 0.001**	
	P-value[c]	**0.036**	0.085	
Physical Function	Baseline	29.49 ± 10.49	29.80 ± 12.25	0.902
	2 weeks	24.88 ± 11.11	24.52 ± 12.88	0.590
	4 weeks	22.17 ± 11.48	20.84 ± 12.00	0.229
	P-value[a]	**< 0.001**	**< 0.001**	
	P-value[b]	**< 0.001**	**< 0.001**	
	P-value[c]	**< 0.001**	**< 0.001**	
Stiffness	Baseline	3.24 ± 2.13	3.05 ± 1.98	0.657
	2 weeks	2.54 ± 2.19	2.64 ± 1.97	0.293
	4 weeks	2.56 ± 2.34	2.09 ± 1.89	0.334
	P-value[a]	**0.003**	0.061	
	P-value[b]	**0.023**	**0.003**	
	P-value[c]	0.999	**0.020**	

P-value[1]: comparison between study groups. P-value[a]: comparison between baseline and 2 week. P-value[b]: comparison between baseline and 4 week. P-value[c]: comparison between 2 week and 4 week.

2.3. Participants

Study participants (both male and female) were included if they were between the age of 30–70 years old. Other inclusion criteria were diagnosis of osteoarthritis according to the suggested criteria by American College of Rheumatology [20] and Kellgren-Lawrence Grading Scale [21] (grade I to III), presence of knee joint pain at least for 3 months, and absence of congenital abnormality of lower extremity. Exclusion criteria were secondary osteoarthritis (rheumatoid arthritis, gout, pseudo gout, infected arthritis, metabolic arthritis and traumatic arthritis), history of joint replacement, concomitant use of glucosamine or chondroitin sulfate, history of knee injection of corticosteroid or hyaluronic acid in the past three months, history of the use of oral or topical analgesic drugs 3 days before enrollment or using oral and topical corticosteroid 14 days before enrollment, pregnancy or lactation, drug abuse, skin lesions of the knee, history of inflammatory bowel disease or peptic ulcer; obesity (BMI ≥ 35 kg/mˆ2); history of the use of physical modalities 2 weeks before enrollment (such as physiotherapy, acupuncture, and transcutaneous electrical nerve stimulator).

2.4. Sesame oil preparation and standardization

Sesame seeds were purchased from a local herbal market in Tehran, Iran. It was authenticated by a botanist. Then, a voucher sample was kept in FUMS herbarium (ID No. FCT-17-43).

The seeds were ground, and then cold-pressed. The resulting oil was subjected to gas chromatographic (GC) analysis. According to GC results, oleic acid (44.01%), linoleic acid (39.11%), palmitic acid (9.23%), stearic acid (5.55%), alpha-linolenic acid (0.33%), and gamma-linolenic acid (0.15%) were the major ingredients of the used oil.

2.5. Intervention and assessment of patients' compliance

After receiving written informed consent from the enrolled patients, they were randomly assigned to receive sesame oil (as the intervention group) or 1% diclofenac sodium gel (as the control group). Patients in the intervention group received topical sesame oil to anoint on the knee (1.5 cc, three times a day) for 4 weeks. In the control group, patients received topical diclofenac sodium gel 1% (Sobhan darou) to anoint on the knee (one fingertip unit, three times a day) for 4 weeks. Maximum daily dose of 200 mg of celecoxib (Tehran darou) divided into two 100 mg capsules was prescribed as a standard treatment for pain relief for both groups. The patients were asked not to change weight by diet or physical activity during the study period. No changes occurred to the trial outcomes after the trial commenced. It should be noted that there were no co-interventions.

Patients' compliance was assessed using telephone survey. Therefore, patients' compliance of more than seventy percent was assured.

2.6. Randomization, allocation concealment, and blinding

One hundred and four eligible OA patients were randomized in two parallel groups. Simple sampling method was used from all patients with knee OA who referred to Hamze orthopedic clinic (affiliated to FUMS), Fasa, Iran. The participants were divided into intervention and

Table 4
Comparison of mean difference of study variables between Sesame oil and Diclofenac gel groups.

		Sesame oil (n = 47)		Diclofenac gel (n = 47)		P-value Mann-Whitney
		Mean	SD	Mean	SD	
Visual analogue scale*	2w - baseline	−7.79	5.62	−7.65	5.50	0.576
	4w - baseline	−13.36	8.94	−14.69	8.35	0.546
Knee flexion angle*	2w - baseline	8.27	22.61	1.82	27.72	0.070
	4w - baseline	12.62	21.66	7.22	23.40	0.151
8-meter walk test	2w - baseline	−0.94	1.77	0.23	1.69	**0.007**
	4w - baseline	−0.67	2.26	0.03	1.86	0.302
Number of analgesic consumption	4w − 2w	−0.39	5.25	3.50	8.54	**0.024**
WOMAC Total*	2w - baseline	−6.83	7.21	−6.98	7.23	0.346
	4w - baseline	−10.04	8.45	−12.17	9.12	0.268
WOMAC Pain*	2w - baseline	−1.51	2.29	−1.30	2.25	0.256
	4w - baseline	−2.04	2.85	−2.26	3.11	0.906
WOMAC Physical function	2w - baseline	−4.61	5.51	−5.27	5.48	0.961
	4w - baseline	−7.32	5.68	−8.95	6.65	0.383
WOMAC Stiffness	2w - baseline	−0.71	1.27	−0.41	1.13	0.168
	4w - baseline	−0.68	1.56	−0.95	1.79	0.433

Asterisked variables were computed for each knee of patients and the others for each patients.
Safety and tolerability.
No adverse event (neither serious nor minor) was reported by patients in both groups of the study during the trial period.

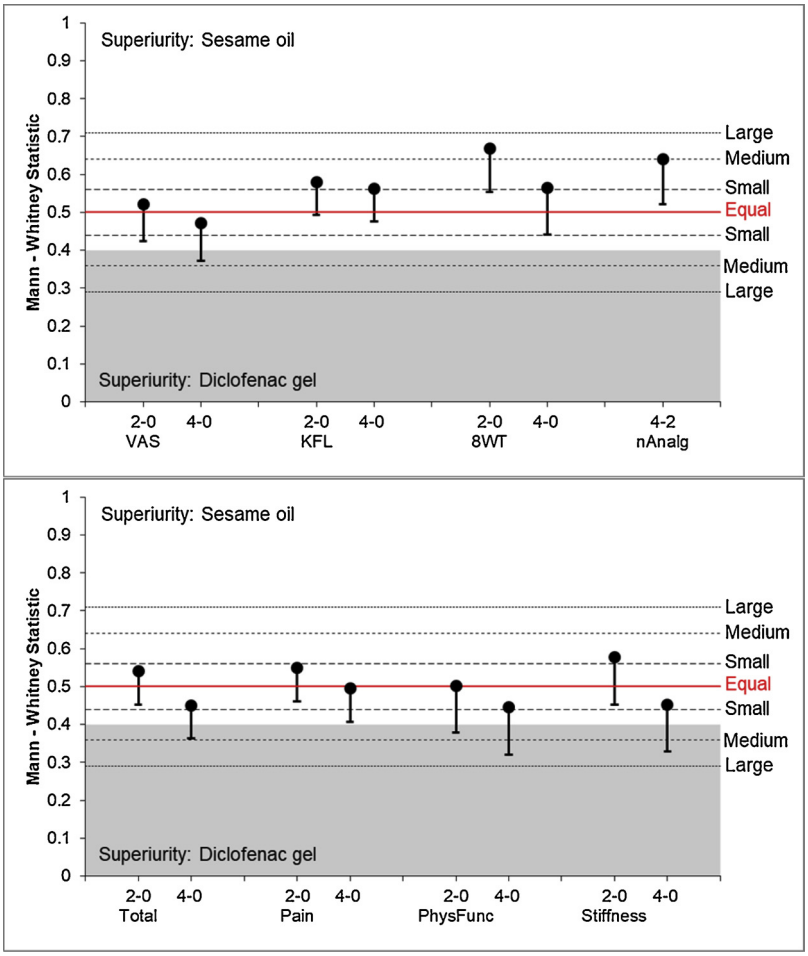

Fig. 2. Sesame oil vs. diclofenac gel: effect sizes (Mann–Whitney) and one-sided 97.5% CI for visual analogue scale (VAS), knee flexion angle (KFL), 8-meter walk test (8WT) and number of consumed analgesics (nAnalg) (Upper chart); and for total, pain, physical function and stiffness score of WOMAC (Lower chart).
The shaded area is below of non-inferiority margin (0.4). Non-inferiority of sesames oil happens when lower bond of confidence interval is upper than shaded area (Non-inferiority margin).
The 2-0 (4-0) means difference of 2 (4) week from baseline. The 4-2 means difference of 4 week from 2 week measurement.

control groups via blocked randomization method (non-stratified, four patients in each block). Randomization list was generated by a biostatistician using Microsoft Excel® software.

Additionally, participants were assigned to the study groups by the secretary of the clinic using sequentially numbered opaque and sealed envelopes which contained letters A and B, indicating the intervention and control groups, respectively. Therefore, allocation concealment was guaranteed.

Sesame oil was prepared in the same containers as diclofenac gel, so that the appearance of the tubes was completely identical and the physicians, outcome assessors, and patients did not know the contents of the drug. Additionally, the drugs were given by a third person (who was not involved in the research) to the patients.

2.7. Outcomes

Primary outcome measure of this clinical trial was the total Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score. WOMAC is a valid questionnaire that has been used in so many studies on OA [22] The secondary outcome measures included the patients' knee joint physical function and stiffness assessed by the WOMAC questionnaire, knee joint pain evaluated by visual analogue scale (VAS), and also by WOMAC questionnaire. It should be noted that VAS is a valid tool for chronic pain assessment.[23] In addition, knee flexion angle (by using of standard goniometer) as another reliable and valid measure,[24,25] 8-meter walk test [which is reliable and valid test in patients with OA [26,27] measuring the required time for walking on a standard flat surface of 8 m], and celecoxib consumption rate were the other secondary outcome measures. All of the study outcome measures were assessed by a physician in the Hamze clinic at the baseline, and then every two weeks. No changes to trial outcomes were made after the trial commenced.

2.8. Statistical analysis

For the comparison of the mean changes of knee joint pain intensity according to the VAS score, the sample size was calculated by considering power 95% and type 1 error 5% based on previous similar study [18]

Data were presented as the mean and standard deviation (SD). Two WOMAC sub-scores -stiffness and physical function-, the speed of walking and the number of consumed analgesics were assessed for each patient. These variables, during three measurement times, were analyzed separately in each group using Repeated Measurement ANOVA followed by Bonferroni post hoc test. Comparison of these variables before the intervention was done by t-test. Also, comparison of them at 2 and 4 weeks after the intervention was done with ANCOVA. The last analysis was adjusted by baseline measurement as the covariate. Moreover, all of dropped-out cases occurred before the first follow-up visits. Therefore, we had no intention-to-treat analysis.

In the variables evaluated separately for each knee -two measurements for each patient including VAS and knee flexion angle-, pain and the total score of the WOMAC questionnaire, generalized estimate equation (GEE) model with unstructured correlation matrix were performed for analysis of the data. GEE is a quasi-likelihood approach for correlated data which does not fully specify the distribution of responses in each patient as a cluster [28] The difference of the above-mentioned variables in three times was analyzed separately in both groups. In this analysis, three measurement times and two knees of each patient were treated as correlated. The baseline comparison between the study groups was performed in another GEE model in which the two knees were treated as correlated and study group as the independent effect factor. The comparison of the study groups at 2 and 4 weeks after the intervention was done with two other GEE models. In the last models, the knees were treated as correlated, baseline measurement as the covariate, and the study group as the independent effect factor.

The non-inferiority effects of sesame oil vs. diclofenac gel was investigated using a test for non-inferiority. Effect size analyses were made by applying the Wilcoxon–Mann–Whitney (MW) test. It provides the common language effect size with MW estimator [29] The confidence interval for MW estimator were computed from Sen's introduced method [30] from.[31] The relevant benchmarks for the MW estimator were: 0.29 = large inferiority, 0.36 = medium-sized inferiority, 0.44 = small inferiority, 0.50 = equality, 0.56 = small superiority, 0.64 = medium-sized superiority and 0.71 = large superiority.[32] Non-inferiority was shown if the lower bound of the confidence interval was lying above the predefined non-inferiority margin of 0.4.

The statistical analyses were performed using IBM SPSS 24 (IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp.). Confidence interval for MW estimator was calculated using R 3.5.0 software (R Core Team, 2018. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/). Figure was drawn using MS Excel 2010 (Microsoft Corp, Redmond, WA, USA). A P-value less than 0.05 was considered as significant.

3. Results

From December 2017 to March 2018, a total of 147 patients were assessed for eligibility. One hundred and four of them were eligible and willing to participate, so they were included in the trial. Fifty two patients were allocated to the intervention group and the other 52 patients comprised the control group. Fig. 1 is a flow diagram of the patients' screening, enrollment, allocation, follow-up, and analysis.

The mean age of the participants in the study was 57.5 ± 12.5 and 57.5 ± 9.1 years in sesame oil and diclofenac groups, respectively. This did not show a significant difference between the two groups of the study (p = 0.976). None of the demographic data and baseline clinical characteristics of the participants showed a significant difference between the two groups. Details of the baseline demographic and clinical data of the patients were presented in Table 1.

We observed a significant reduction in the pain of patients represented by the VAS score compared with the baseline in both groups of the study after two weeks that was not significantly different between the two groups. Also, within group changes in both of the groups remained statistically significant ($P < 0.001$) at the end of the study (Table 2).

It seems that patients in both of the study groups experienced improvement of their knee flexion range, regarding within groups comparison. However, there was no between group differences. Speed of walking, as another indicator of the patients' knee joint functionality, showed no between group differences, except for the 2 week value ($P = 0.011$). Also, the only within group significant difference was an increase in the speed of walking in the sesame oil group at 2 weeks ($P = 0.001$) (Table 2).

The mean number of analgesics consumed by the patients in the diclofenac group was significantly lower when compared to the sesame oil group at the end of the 2nd week ($P = 0.04$). However, the consumed analgesics in the sesame oil group compared to the diclofenac group significantly decreased at the end of the 4th week ($P = 0.022$) (Table 2).

Regarding the total WOMAC and its three domains scores, there was no significant difference between the two groups of the study (Table 3). However, the patients obtained a significant improvement regarding within group analysis of the total WOMAC and its three domains scores in both groups of the study (Table 3).

3.1. Non-inferiority comparison

Within the 2-week intervention period, the mean value of the VAS decreased 7.79 mm in the sesame oil and 7.65 mm in the diclofenac gel group (Table 4). Non-inferiority of sesame oil was demonstrated (MW = 0.522; CI-LB = 0.424). Also, at the 4th week the mean VAS score decreased 13.36 mm in the sesame oil and 14.69 mm in the diclofenac gel group. Opposite, non-inferiority of sesame oil could not be approved (MW = 0.472; CI-LB = 0.372) (Fig. 2). Within the 2-week intervention period, regarding knee flexion angle (MW = 0.580; CI-LB = 0.494) and 8-meter walk test (MW = 0.668; CI-LB = 0.554), non-inferiority of sesame oil was demonstrated. It also approved at the 4-week intervention time for both of the measurements (MW = 0.563; CI-LB = 0.477 and MW = 0.565; CI-LB = 0.442 for knee flexion angle and 8-meter walk test, respectively). Additionally, after the 4-week intervention period, the mean number of consumed analgesics decreased 0.39 in the sesame oil group and increased 3.5 in the diclofenac gel group (Table 4). Therefore, non-inferiority of sesame oil was demonstrated (MW = 0.641; CI-LB = 0.521).

Regarding WOMAC pain score, non-inferiority of sesame oil was approved within the 2 and 4-week intervention period (MW = 0.549; CI-LB = 0.461 and MW = 0.495; CI-LB = 0.407 for 2 and 4 week, respectively). While, WOMAC physical function score did not demonstrated the non-inferiority of sesame oil at both 2- and 4-week intervention period (MW = 0.503; CI-LB = 0.378 and MW = 0.445; CI-LB = 0.321 for 2 and 4 week, respectively). Finally, stiffness sub-score and total score of WOMAC demonstrated the non-inferiority of sesame oil at 2-week intervention period (MW = 0.577; CI-LB = 0.452 and MW = 0.541; CI-LB = 0.453 for stiffness and total WOMAC score, respectively). However they both could not approve the non-inferiority of sesame oil at 4-week observation period (MW = 0.452; CI-LB = 0.329 and MW = 0.450; CI-LB = 0.364 for stiffness and total WOMAC score, respectively) (Fig. 2).

4. Discussion

In the present trial, we evaluated the efficacy of sesame (*Sesamum indicum* L.) oil on knee OA via a randomized double-blinded active-controlled non-inferiority clinical trial. Generally, it seems that topical use of sesame oil was non-inferior to diclofenac gel regarding the reduction of the knee OA pain. Also, according to the findings it was non-inferior regarding some indicators of functionality of the patients which were related to knee OA. However, sesame oil was inferior to diclofenac gel in term of patients' physical function score of WOMAC.

To the best of our knowledge, this trial is the first clinical trial that examined effectiveness of the topical sesame oil in OA patients. Although there were several preclinical studies on the effectiveness of sesame and its derivatives, especially sesamin in different diseases, there were few clinical data about its role in OA [15,33]

Previous animal studies pointed out anti-inflammatory beneficial effects of sesame and suggest its potential roles in the prevention and treatment of OA. Kong et al. evaluated the anti-inflammatory effects of sesamin on IL-1β-stimulated human osteoarthritis chondrocytes[2] They have demonstrated that sesamin treatment significantly inhibited the PGE2 and NO production induced by IL- 1β. They suggested that sesamin showed anti-inflammatory effects on IL-1β-stimulated

chondrocytes by activating Nrf2 signaling pathway. Since IL-1β is one of the important cytokines in the progression of OA and could induce the production of inflammatory mediator PGE2 and NO production in chondrocytes, inhibition of IL- 1β-induced inflammatory response by sesamin may be a helpful strategy to prevent or treat OA.[2]

Oxidative stresses and muscular dysfunctionis are the other factors involved in the pathogenesis of OA and may precede the onset of radiographic evidence of OA and pain [34] Dur-Zong et al. showed sesame oil decreased the muscular interleukin-6 and increased the citrate synthase activity and myosin heavy chain IIa mRNA expression. They also found that sesame oil decreased the muscular lipid peroxidation, nuclear Nrf2 protein expression, and reactive oxygen species generations in addition to increased glutathione production and glutathione peroxidase activity in OA rats. They concluded that daily sesame oil supplement may attenuate the early joint pain by inhibiting Nrf2-associated muscular oxidative stress in OA rat model.[15] Since topical sesame oil was used in our study, the possibility of the effectiveness of sesame oil with the mechanism of action described in Dur-Zong's study was strengthened.

Interestingly, another study evaluated the effects of sesame seed supplementation on clinical signs and symptoms in patients with knee OA via a randomized controlled clinical trial. It showed that dietary sesame (40 g/day) supplementation led to improved clinical symptoms in patients with knee OA which is compatible with our results [14]

There are several limitations regarding external validity and applicability of our findings:

We had no mechanistic assay about the efficacy of topical sesame oil on OA. However, there were different previous studies about the efficacy of sesame on OA (from animal studies to clinical trials on oral consumption of sesame in OA). Lack of placebo comparator group was another methodological limitations in this study. Indeed, we could discuss better about the effectiveness of sesame oil in OA by including a placebo group. Short-term follow up of the patients was another arguable issue of the study. Because OA has a chronic nature, by extending the study period we can also evaluate the recurrence of the symptoms or might make the adverse events of sesame oil known. Moreover, small sample size was another important limitation of the current study. Finally, there are two points which should be considered regarding generalizability of the results: first, patients' mean BMI was not normal in both of the groups (they were overweighed). However, possibly efficacy of topical drugs may have lower association to factors like BMI. The second, was the patients' mean duration of knee OA. It was more than 6 years. Patients with new onset knee OA may have different response to the sesame oil or diclofenac gel.

5. Conclusion

According to the results of this clinical trial, it seems that topical use of sesame oil was non-inferior to diclofenac gel regarding the reduction of the knee OA pain. According to the findings, it was also non-inferior to diclofenac gel regarding some indicators of functionality of the patients (i.e. 8-meter walk test but not WOMAC physical function score) which were related to knee OA. Additionally, it had a relative non-inferiority to topical diclofenac regarding patients' knee joint stiffness (not for WOMAC stiffness score at 4th week). Finally, it should be noted that sesame oil was not inferior to diclofenac gel in term of the number of consumed analgesics.

Declaration of Competing Interest

The authors have no conflicts of interest to declare. The funding organization had no role in study design; data collection and analysis; interpretation of data; manuscript preparation; or decision to submit results for publication.

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