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Original Article

Effect of topical *Cichorium intybus* gel on knee osteoarthritis: A randomized, double-blind, placebo-controlled trial

Sadra Ansaripour[1], Farinaz Farahbod[2], Siavash Fazelian[3], Afsaneh Malekpour-Tehrani[4], Morteza Dehghan[3*]

[1]Student Research Committee, Shahrekord University of Medical Sciences, Shahrekord, Iran
[2]Department of Obstetrics and Gynecology, Isfahan University of Medical Sciences, Isfahan, Iran
[3]Clinical Research Development Unit, Kashani Hospital, Shahrekord University of Medical Sciences, Shahrekord, Iran
[4]Department of Social Medicine, Shahrekord University of Medical Sciences, Shahrekord, Iran

*Corresponding Author: Morteza Dehghan, E-mail: dehghan_mortaza@yahoo.com

Abstract

Background and aims: The existing evidence indicates the adverse effects of oral non-steroidal anti-inflammatory drugs (NSAIDs) on reducing pain associated with knee osteoarthritis (OA). This study aimed to investigate the effect of the herbal drug *Cichorium intybus* gel and diclofenac gel on pain reduction, morning stiffness, and physical function in knee OA patients.

Methods: In a randomized, double-blind clinical trial, 150 patients with moderate to severe knee OA without comorbidity were randomized to one of three groups (A, B, and C). Then, patients were treated with one fingertip unit per 25 cm^2 of the skin of 3% hydroalcoholic *C. intybus* extract gel, diclofenac gel, and placebo gel three times a day for six days. The therapeutic response was evaluated using standard measures.

Results: *C. intybus* gel and diclofenac gel could significantly reduce the visual analogue scale score and Western Ontario and McMaster Universities Arthritis Index score, including total pain, physical function, and morning stiffness ($P<0.001$) in comparison with the control group. The effect of *C. intybus* gel and diclofenac gel was not significantly different ($P>0.05$). No serious adverse effects were observed based on the findings.

Conclusion: *C. intybus* extract gel as an alternative herbal remedy can be further investigated given its efficacy, which is better than placebos and similar to diclofenac.

Keywords: Osteoarthritis, Knee, *Cichorium intybus*, Herbal medicine, Diclofenac

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Introduction

Osteoarthritis (OA) is the most common articular disorder. Although the destruction of articular cartilage is the main feature of OA, destruction of other articular tissues, including synovial membrane and subchondral bone, actively contribute to its progression (1). The intensification of the progression of OA makes it among the 20 leading diseases in the age group of 40-45, and the resulting disability, especially in the elderly, has a tremendous effect on individuals and society (2,3). The prevalence of knee OA in Iran is about 19%, which is higher than its global prevalence of 16% (4,5).

The pathogenesis of the disease is multifactorial, and systemic risk factors such as age, race, gender, and genetics, as well as topical risk factors such as obesity, anatomical anomalies, previous trauma, and occupation, contribute to the disease development (6).

The symptoms of OA widely vary among patients and can include pain and stiffness in the joints, swelling, decreased function, cracking, and noisy joints (7). These symptoms usually slowly change and intensify over a long period. Short-term morning stiffness, functional limitation, and one or more symptoms in clinical examination (e.g., crepitation, limitation of motion, and bony outgrowths) are observed in adults over 40 with knee pain (7,8).

The goal of treatment in patients with OA is to reduce pain and other symptoms associated with the disease and, ultimately, to improve the individual's functional capacity. There are several therapies for knee OA, such as lifestyle modification, drug therapy, physiotherapy, and surgical interventions, among which drug therapy is the most commonly used one (9). Existing treatments reduce symptoms and relieve severe pain. Meanwhile, the effects of placebo have been reported to be remarkably similar to those of many treatments, including acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase-2 (COX-2) inhibitors, hyaluronic acid, and glucosamine (10). There are many challenges about the side effects of drugs, especially in the elderly, which has increased the willingness of such patients to take complementary and alternative medicines (10).

Due to limitations associated with the use of NSAIDs, the use of alternative therapies, such as medicinal plants, is increasing, including an old plant called chicory (*Cichorium*

intybus L.), a diploid species belonging to the Asteraceae family (10). A previous pilot study showed that the 1,800 mg/day chicory root extract could improve the pain and stiffness of patients with OA of the hip or knee (11).

Chicoric acid is the main compound of the *C. intybus* methanolic extract. Moreover, aliphatic compounds and their derivatives are the main components, and terpenoids account for a small part of the plant. The flower of this plant contains saccharides, methoxycoumarin cichorine, and flavonoids (12). Chicory leaves are good sources of anthocyanins and vitamins A and C that stimulate the immune system and limit infection and inflammation (13). Due to numerous polyphenols, this plant has antioxidant properties, so its powder reduces hepatotoxicity and increases resistance to oxidative stress caused by nitrosamine precursors (14).

Despite the traditional use and laboratory studies for the anti-inflammatory and analgesic effects of the *C. intybus* extract, there is no human evidence to evaluate its traditional use in patients with OA. Therefore, this randomized, placebo-controlled clinical trial investigated the efficacy and safety of *C. intybus* hydroalcoholic extract gel in OA patients with knee pain.

Materials and Methods

Study design

This double-blind, placebo-controlled clinical trial was conducted in 2018-2019 at Shahrekord University of Medical Sciences. In addition, the study method was the same after the start of the intervention.

Sample size

The sample size was calculated at 50 for each group according to similar studies and using SPSS24 software, given a 95% confidence interval and 5% error, and the mean of pain in the study of Dehghan et al, which was 14.85 ± 5.02 in the studied group and reached 3.57 ± 2.6 (15).

Inclusion and exclusion criteria

Patients aged 45-75 years with symptoms of primary OA have been presented according to the American College of Rheumatology's diagnostic criteria that indicate the definitive diagnosis of rheumatoid arthritis depends on having a score of 6 or more than ten based on the type of joints involved, the acute phase reactants, and the duration of the disease (16). Those who did not have liver, kidney, and underlying diseases or any history of allergy according to the diagnosis of a specialist doctor were enrolled after providing informed consent to participate in the study (14).

The exclusion criteria included a history of allergy to any form of anti-inflammatory drugs, skin diseases or infections, or ulcers at the site of topical application of the studied medicine, the use of other topical medications at the site of topical application of the studied drugs, and the use of aromatase inhibitors. The other exclusion criteria were the oral administration of other anti-inflammatory drugs and other compounds effective in the treatment of OA up to 10 days before the beginning of the study, congenital articular diseases, pregnancy, lack of cooperation during the study, and any allergies or problems during the study.

Intervention

In this study, 150 individuals referred to the University Clinic and private clinics, who fulfilled the inclusion criteria, were selected by convenience sampling and then enrolled. All participants received the necessary training before participating in the trial and received the required study sheets stating the goals and procedure of the study. To control the pain of patients during the study period and not deprive them of treatment due to ethical considerations, 200 mg/kg celecoxib capsules were daily prescribed in addition to topical gel for each of the three groups.

All patients were treated with one of the treatment groups, namely, 3% *C. intybus* hydroalcoholic extract gel, 1% diclofenac gel, and placebo gel, for six weeks. During this period, the patient was asked to apply the gel in the site of interest for one fingertip unit per 25 cm^2 of skin for 3-5 minutes 3 times a day (according to the training given to them before the clinical trial). All patients were examined before and after the treatment and completed the visual analogue scale (VAS), the Valid Western Ontario and McMaster Universities Arthritis Index (WOMAC), and the demographic checklist. Valid WOMAC was applied to assess dimensions of pain, joint stiffness, and disability in knee OA (17). VAS has been validated in previous studies by owners to measure chronic pain (18).

Randomization and blinding

The gels were made by a pharmacognosist and packaged in identical tubes. The tubes were labeled with letters A, B, and C and delivered to the researcher so that the patients and the researcher did not know the content of any of the tubes. A randomized block design randomly assigned patients to one of 50 A, B, or C groups. Then, they received the tube gel with the same name as the chosen group.

Preparation and identification of plant and extract

The aerial part of the *C. intybus* plant was registered as code 148 by a botanist after collecting, identifying, and confirming at the Herbarium Center of Medical Plants Research Center of Shahrekord University of Medical Sciences.

The plant's aerial parts were powdered using a grinding device. Then, 500 g of the powder was poured into an Erlenmeyer flask, and 70% ethanol was added. The mixture was finely stirred using a magnetic stirrer. After 72 hours, the transparent extract obtained from the powder was filtered with filter paper (Whatman filter paper grade 40). The solution was condensed by a rotary device at 40 °C and 50-100 rpm for 3-4 hours. Next, pharmacologists used the thin-layer chromatography method to standardize based on *C. intybus* (19). Concentrated extracts were left in a 37

°C incubator to evaporate the additional solvent to obtain dry matter, which was used to prepare the gel (20).

Preparation of dry extract gel

For preparing a 3% *C. intybus* gel, 3 g of dried hydroalcoholic extract, after weighing, was well solved in 1% Carbopol gel base, and a completely transparent gel was obtained. Finally, 0.1% propylparaben ($C10H1_2O_3$) was added to the final formulation, which prevented the growth of the fungus and bacteria in the gel. The resulting gel was prepared, packaged by the pharmacist, and used for the next steps. These identical opaque tubes weighed 50 g and were named A, B, and C.

Evaluation of treatment efficacy

Assessment of the severity of the patient's pain using the VAS criteria

The VAS of the pain, or the pain ruler, includes a horizontal line scaled from 0 to 10, indicating absolute analgesia and unbearable pain, respectively. Scores of 1-3, 4-7, and 8-10 mean mild, moderate, and severe pain, respectively.

Evaluation of the effect of pain on patient functioning according to WOMAC Criteria

In the WOMAC, knee pain, morning stiffness, daytime stiffness, and physical function were evaluated using 24 items. In this scale, the pain variable is measured by five items (scored 0-20), and joint stiffness and physical function are estimated by two and 17 items, respectively (scored 0-68 and 0-8).

Safety measurement

All participants of the three interventions were screened by a checklist including several questions about different organs (e.g., gastrointestinal, skin, nervous, and respiratory complaints) to identify possible side effects.

Statistical analysis

The means and standard deviations (SD), as well as the qualitative data, frequencies, and percentages, were used to describe the quantitative data. The chi-square test was utilized to compare the qualitative data. The analysis of variance was employed for quantitative data with normal distribution, and the Kruskal-Wallis test was applied for quantitative data with non-normal distribution. The post hoc test was performed using the Bonferroni test. A paired *t* test was used to compare the quantitative data if normally distributed before and after the intervention. The Wilcoxon signed-rank test was utilized to compare the quantitative data if they were non-normally distributed before and after the intervention. The significance level was considered < 0.05, and data were analyzed by SPSS, version 24.

Results

Study flow and baseline characteristics of participants

Patients were assessed and registered in January 2018 and continued until March 2019. Of the 150 patients aged 45-75 years who participated in this study, 144 cooperated with the research and completed the treatment course. Of the 144 patients, 49 (40 women and 9 men) in group A (34%) received *C. intybus* extract gel 3%, 46 (32 women and 14 men) in group B (31%) received a placebo, and 49 (30 women and 19 men) in group C (34%) received diclofenac 1% gel (Figure 1).

No significant statistical difference was observed in

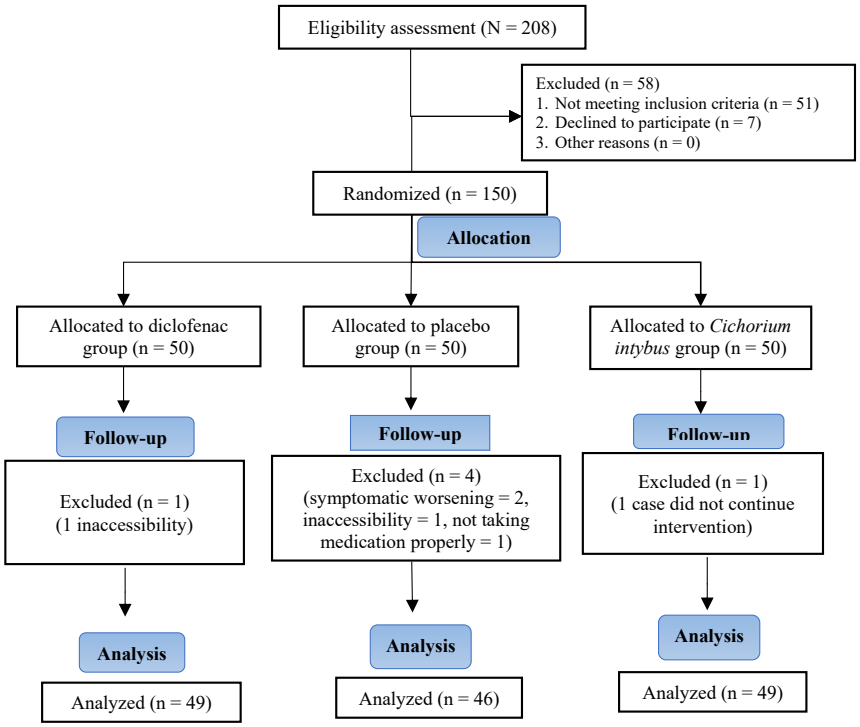

Figure 1. The flowchart of the trial

demographic information, including age, gender, marital status, occupation, and education among the groups, indicating the appropriate distribution of the participants in this clinical trial ($P<0.05$). Based on the Kruskal-Wallis test results, the difference in mean body mass index (BMI) was not statistically significant among the A, B, and C groups ($P=0.059$, Table 1).

Clinical responses

Table 2 provides the results of improving the symptoms

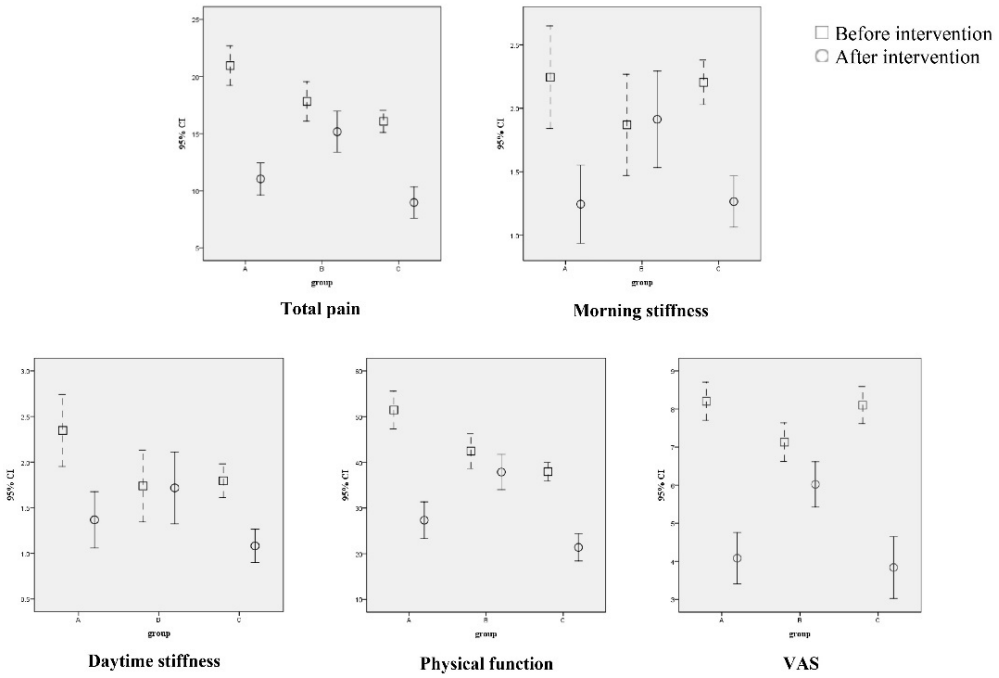

Figure 2. Error bars of evaluation variables before and after intervention in the studied groups in week 6. *Note*. VAS: Visual analogue scale; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; CI: Confidence interval; Group A: 3% *Cichorium intybus* extract gel, Group B: Placebo gel, and Group C: 1% diclofenac gel. WOMAC pain scale=0–20; Physical function scale=0–68. The significance level for the difference between the groups was considered 0.05

Table 1. Demographic characteristics of participants

Variables		Groups			Total (n=144)	*P* value*
		Group A (n=49)	Group B (n=46)	Group C (n=49)		
Age (y)	45-54, n (%)	18 (36.7)	16 (34.8)	21 (42.9)	55 (38.2)	0.134
	55-64, n (%)	23 (46.9)	20 (43.5)	12 (24.5)	55 (38.2)	
	65-75, n (%)	8 (16.3)	10 (21.7)	16 (32.7)	34 (23.6)	
	Total, n (%)	49 (100)	46 (100)	49 (100)	144 (100)	
Gender	Female, n (%)	40 (81.6)	32 (69.6)	30 (61.2)	102 (70.8)	0.082
	Male, n (%)	9 (18.4)	14 (30.4)	19 (38.8)	42 (29.2)	
	Total, n (%)	49 (100)	46 (100)	49 (100)	144 (100)	
Marital status	Single, n (%)	0	1 (2.2)	1 (2)	2 (1.4)	0.592
	Married, n (%)	49 (100)	45 (97.8)	48 (98)	142 (98.6)	
	Total, n (%)	49 (100)	46 (100)	49 (100)	144 (100)	
Job	Housekeeper, n (%)	39 (79.6)	30 (65.2)	29 (59.2)	98 (68.1)	0.281
	Employee, n (%)	1 (2)	3 (6.5)	2 (4.1)	6 (4.2)	
	Self-employment, n (%)	5 (10.2)	8 (17.4)	14 (28.6)	27 (18.8)	
	Retired, n (%)	4 (8.2)	5 (10.9)	4 (8.2)	13 (9)	
	Total, n (%)	49 (100)	46 (100)	49 (100)	144 (100)	
Education	Under diploma, n (%)	39 (79.6)	37 (80.4)	37 (75.5)	113 (78.5)	0.904
	Diploma, n (%)	6 (12.2)	7 (15.2)	8 (16.3)	21 (14.6)	
	Academic, n (%)	4 (8.2)	2 (4.3)	4 (8.2)	10 (6.9)	
	Total, n (%)	49 (100)	46 (100)	49 (100)	144 (100)	
BMI (kg/m^2), Mean±SD		28.51±4.16	28.75±3.09	27.36±1.97	28.2±3.24	0.059

Note. Group A: 3% *Cichorium intybus* extract gel, Group B: Placebo gel, and Group C: 1% diclofenac gel. SD: Standard deviation; BMI: Body mass index. * The significance level for the difference between the groups was considered 0.05.

Table 2. Treatment Variables Before and After Treatment

Variables		Groups			*P* value
		Group A (n=49)	Group B (n=46)	Group C (n=49)	
Total pain	Before intervention	18.12±3.96	17.59±5.3	16.16±3.27	0.066
	After intervention	10.9±4.7[a]	14.96±5.73[b, c]	8.86±4.56[a]	<0.001
	P value	<0.001	<0.001	<0.001	-
Morning stiffness	Before intervention	2.24±1.41	1.87±1.34	2.2±0.61	0.312
	After intervention	1.24±1.07[a]	1.91±1.28[b, c]	1.26±0.7[a]	0.008
	P value	<0.001	0.527	<0.001	-
Daytime stiffness	Before intervention	2.04±1.24	1.72±1.29	1.65±0.63	0.159
	After intervention	1.2±0.89	1.63±1.24[b]	1±0.67[a]	0.022
	P value	<0.001	0.435	<0.001	-
Physical function	Before intervention	42.04±7.57	40.65±10.44	38.84±5.99	0.055
	After intervention	26.08±10.87[a]	36.8±11.81[b, c]	21.7±9.83[a]	<0.001
	P value	<0.001	<0.001	<0.001	-
Total WOMAC	Before intervention	68.86±16.4	62.89±19.02	61.75±11.63	0.067
	After intervention	40.98±20.13[a]	56.67±20.36[b, c]	32.71±15.89[a]	<0.001
	P value	<0.001	<0.001	<0.001	-
VAS	Before intervention	8.27±1.65	7.61±1.41	8.08±1.66	0.093
	After intervention	4.24±2.3[a]	8.87±1.88[b, c]	3.96±2.53[a]	<0.001
	P value	<0.001	<0.001	<0.001	-

Note. VAS: Visual analogue scale; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index. Group A: 3% *Cichorium intybus* extract gel, Group B: Placebo gel, and Group C: 1% diclofenac gel. [a] A significant difference with a placebo; [b] A significant difference with diclofenac; and [c] A significant difference with *C. intybus*.

of primary knee OA after six weeks of treatment with *C. intybus* extract gel. Based on the Kruskal-Wallis test results, the difference was significant in all variables between the three groups after the intervention ($P=0.008$, $P=0.022$, and $P<0.001$ for morning stiffness, daytime stiffness, and other variables, respectively).

In patients treated with *C. intybus* gel, all variables, except for daytime stiffness, had significantly lower scores compared to the placebo group based on the final evaluation using the post hoc test ($P<0.001$ for physical function score and WOMAC total score, $P=0.001$ for real pain, $P=0.003$ for VAS, $P=0.009$ for morning stiffness, and $P=0.098$ for daytime stiffness). Based on the Post Hoc test results, all variables were significantly lower in the diclofenac group after the intervention compared to the placebo group ($P=0.012$, $P=0.007$, and $P<0.001$ for morning stiffness, daytime stiffness, and other variables, respectively). In addition, the results of this test revealed that the activities of *C. intybus* extract gel and diclofenac gel were similar, with no significant difference between the two groups ($P>0.05$). In the *C. intybus* and diclofenac groups, based on the Wilcoxon test results, all VAS and WOMAC scales decreased significantly after treatment compared to baseline ($P<0.001$, Figure 2).

Short-term safety and tolerability

Chicory gel was not only as well tolerated as diclofenac gel, but no systemic and topical complications were reported in follow-ups and examinations; further, in reducing knee pain, it was highly accepted by the patients.

Discussion

This study aimed to investigate the effect of the herbal drug Cichorium intybus gel and diclofenac gel on pain reduction, morning stiffness, and physical function in knee OA patients. Because older people often suffer from common diseases, they need to take different medications, which may be problematic. For example, in some cases, NSAIDs neutralize the antihypertensive effects in patients with coronary heart disease or cause nephropathy in diabetic patients, or COX-2 inhibitors increase the risk of cardiovascular diseases (21). Therefore, many of these problems can be eliminated by changing the approach from oral and inhaled drugs to topical drugs (21). According to a review of studies, this is the first clinical trial on the properties of *C. intybus* as a prescription medicinal gel for OA treatment (22). The topical use of *C. intybus* gels three times a day for six weeks has clinically improving effects on the complications of knee OA. This study investigated the impact of *C. intybus* gel on pain reduction in patients with knee OA using the pain measures VAS and WOMAC. According to these standard scales, the results showed a significant and substantial reduction of pain as the first result of the effectiveness of using *C. intybus* extract gel during 42 days of treatment (22).

It has been reported that the VAS indicates the severity of objective symptomatic pain in patients with chronic diseases, such as OA. At the same time, WOMAC is mainly used for the functional assessment of pain (23). Regarding the average pain score of patients participating in the study on the VAS at baseline [7.99±1.59], patients

with moderate to severe pain were enrolled in this study.

One of the common treatments for knee OA is diclofenac gel, which is an effective treatment and has been found to produce an analgesic effect in several studies (24). Therefore, one group followed the abovementioned treatment, and the other groups were treated with chicory gel and a placebo. Amorndoljai et al, comparing the effects of the ginger extract and diclofenac 1% on knee OA, found that the ginger extract in the 12 weeks of treatment and during the three stages of the study could decrease the pain according to the WOMAC scale compared to baseline. Their evaluations demonstrated the most improvement in pain, morning stiffness, and physical function. This reduction was reported to be over 50% (25). In our study, as with the mentioned study, pain, morning stiffness, and physical function scores after intervention were significantly lower in the *C. intybus* and diclofenac topical gel groups compared to the placebo group; even in some items such as pain reduction and physical function in the WOMAC scale, *C. intybus* gel had a higher efficacy compared to diclofenac gel. Regarding the side effects of NSAIDs, especially in systemic administration, and the impact of *C. intybus* gel on pain reduction based on the VAS and WOMAC scales, the *C. intybus* topical gel can be considered effective in this treatment. Although the patients were advised to use celecoxib in addition to topical gels, most of them, especially in the *C. intybus* and diclofenac groups, had not used this medication; therefore, statistical analysis of the consumption rate of celecoxib and comparison between groups was impossible.

Studies have shown that various types of immunostimulant polysaccharides in herbal products, such as glucans and mannans, have demonstrated anti-inflammatory activity in the body after oral administration (26). Madhu et al, who reported similar results regarding the effect of the turmeric extract on the treatment of painful knee OA, stated that despite short-term treatment, polysaccharides in the plant extract contributed to pain relief (27). Sun et al investigated the polysaccharides in the *C. intybus* leaf, observing that the leaves of this plant contain large amounts of the polysaccharides glucose and mannan (28). Therefore, these polysaccharides can represent one of the anti-inflammatory mechanisms of *C. intybus* through which the extracted gel acts.

Rafraf et al, examining the pomegranate peel hydroalcoholic extract for the treatment of knee OA, observed a significant difference in the pain level after treatment and baseline pain level and the anti-inflammatory. In addition, the analgesic effects of the extract were attributed to the presence of phenolic, flavonoid, and terpenoid compounds, as the pomegranate peel has been shown to contain high levels of flavonoids and terpenes, which have anti-inflammatory effects. Furthermore, the effects of flavonoids are attributed to the direct involvement of these compounds in the prostaglandin system (29). In an experimental study, treatment with flavon supplements caused a significant decrease in metalloproteinase 3 in the cartilage matrix, preventing collagen degradation and thereby improving articular cartilage in rabbits with OA (30). In a double-blind study, Jabbari et al compared the effectiveness of *Sambucus ebulus* L. and diclofenac gel. Although the mechanism of the effect of herbal treatments has not been entirely determined, the potential mechanisms that can produce analgesic effects, according to the VAS and WOMAC measures, are related to phytochemical compounds of the plant, including quercetin, glycosides, ebulitin, flavonoids, and anthocyanins (31). The mechanism of the effect of flavonoids, which include a wide range of different compounds, is probably related to the inhibition of the activity of the inflammatory enzymes or the inactivation of prostaglandins. These compounds have antioxidant properties and, by inhibiting catechol-O-methyltransferase, protect catecholamines, which is the most critical anti-inflammatory property of flavonoids (32,33). The *C. intybus* extract also contains terpenoids, saccharides, flavonoids, and aliphatic compounds and their derivatives that prevent the formation of destructive free radicals for cartilage tissue by exerting antioxidant effects (33). According to those mentioned above, it is possible to attribute the relief of the inflammation and pain associated with using the *C. intybus* extract to the existing flavonoids, which can prevent the erosion of articular cartilage.

Similarly, Jabbari et al stated that the anti-inflammatory effects of the *Sambucus ebulus* L. extract are due to valuable compounds such as polyphenols and anthocyanins with antioxidant activity. This value is based on the assumption that oxidative stress plays a substantial role in the etiology and exacerbation of OA (31). Oxidative stress by free radicals destroys homeostasis cartilage formation in joints, induces apoptosis in chondrocytes, disrupts cartilage production, and produces excessive reactive oxygen species that cause chronic pain. This can explain the role of reactive oxygen species in OA (34). In addition, free radicals produced by abnormal chondrocytes can damage intra-articular parts and their components, such as proteins, fats, and nucleic acids (35). Therefore, *C. intybus* extract gel, also due to its antioxidant properties, can protect articular cartilage and prevent the progression of OA.

Panahi et al, with the use of curcumin in the treatment of patients with knee OA, attributed the protective effects of this active ingredient on OA to the anti-inflammatory properties of plant-based medicinal compounds, explaining it by inhibiting the critical regulators of inflammation such as lipoxygenase and COX-2 and decreasing the release of inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin 1 (IL-1), IL-6, and prostaglandin E2 (36). The *C. intybus* extract also produces an anti-inflammatory effect by inhibiting COX-2 (37). The root of *C. intybus* has potent anti-inflammatory effects due to its high levels of sesquiterpene lactones, commonly found in plants

from the Asteraceae family (38). These compounds can potentially inhibit prostaglandin E2 synthase by inhibiting the expression of COX-2. It inhibits prostaglandin synthesis dose-dependently (39). Based on the results of a review study by Sharma et al investigating the therapeutic effects of *C. intybus*, *C. intybus* root extract could reduce the production of prostaglandin E2 by directly inhibiting COX-2 and via TNF-α (40). It has also been shown that the root extract of this plant has an anti-inflammatory activity that reduces the level of inflammatory cytokines such as TNF-α, IL-6, and IL-1 while increasing inflammatory enzymes such as catalase and glutathione peroxidase (41). Accordingly, the anti-inflammatory effect of *C. intybus* extract gel is likely applied in four ways, including glucan and mannan polysaccharides, flavonoids, antioxidants, and reduction of inflammatory cytokine levels. However, the totality of these cases can partly explain the functional and complication improvement in patients with knee OA due to treatment with herbal extracts.

Regarding the safety of the extract, Olsen et al, in a double-blind clinical trial, examined the therapeutic effect of *C. intybus* root extract in 40 patients with knee and hip OA and observed that oral administration of *C. intybus* root extract for one month could have a practical impact on pain and stiffness due to OA (11). In one study, the topical use of 3% *C. intybus* extract gel two times a day for 28 days was found to effectively protect against UV radiation without any complications (42). In addition, *C. intybus* is recognized as a frequently used food additive that is highly safe, and its extract has not shown any significant toxicity in the trials. This immune factor can be advantageous for using this herbal substance in oral or prescribed clinical trials. In this study, the *C. intybus* extract gel significantly reduced the pain associated with knee OA without any complications (43).

Limitations of the study

Despite the effectiveness of the chicory gel, some limitations, such as small population size and lack of objective criteria for estimating the performance of the patients, could affect the results and their interpretation. Further, the short duration of the study may demonstrate no long-term complications and side effects in patients.

Conclusion

According to the results of this study, the use of *C. intybus* extract gel had a significant effect on the improvement of the symptoms of the disease. Therefore, it can be used as a natural alternative to the diclofenac gel as a type of synthetic NSAIDs in knee OA patients with mild-to-moderate pain and symptoms. Medicinal plants that affect the treatment of rheumatological diseases, if administered with synthetic drugs, can reduce the dose of these drugs and thereby reduce their side effects. Therefore, the use of herbal medicines in a topical way with precise formulation instead of synthetic drugs can be considered in future studies. Further, measuring changes in blood chemical parameters during treatment should be regarded as in *vivo* studies. The length of the treatment period can affect the results of this study, which may require a more extended treatment period for the drug's effectiveness.

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Authors' Contribution

Conceptualization: Sadra Ansaripour, Afsaneh Malekpour-Tehrani, Morteza Dehghan.
Data curation: Sadra Ansaripour, Morteza Dehghan.
Formal analysis: Afsaneh Malekpour-Tehrani, Siavash Fazelian.
Funding acquisition: Afsaneh Malekpour-Tehrani.
Investigation: Sadra Ansaripour, Morteza Dehghan, Farinaz Farahbod.
Methodology: Afsaneh Malekpour-Tehrani, Siavash Fazelian.
Project administration: Sadra Ansaripour.
Resources: Sadra Ansaripour.
Software: Afsaneh Malekpour-Tehrani.
Supervision: Sadra Ansaripour, Afsaneh Malekpour-Tehrani, Morteza Dehghan.
Validation: Sadra Ansaripour.
Visualization: Sadra Ansaripour, Siavash Fazelian, Morteza Dehghan.
Writing–original draft: Sadra Ansaripour, Siavash Fazelian, Morteza Dehghan, Farinaz Farahbod.
Writing–review & editing: Siavash Fazelian, Morteza Dehghan.

Competing Interests

The authors declare no conflict of interests.

Ethical Approval

The protocol of this study was approved by the University's Deputy of Research and Technology (Ethical Code: IR.SKUMS.REC.1396.154) and registered in the Iranian Registry of Clinical Trials (identifier: IRCT2017103037093N1). This study was performed using the principles of the Declaration of Helsinki.

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