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Efficacy of Topical *Elaeagnus angustifolia* Fruit Extract Gel Add-On Treatment in Knee Osteoarthritis: A Double-Blind Randomized Placebo-Controlled Trial

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ABSTRACT

Background & Objective: Osteoarthritis is the most prevalent cause of joint pain and limited mobility in older adults. It is a degenerative joint disease with inflammatory features. Current treatments mainly alleviate symptoms but do not halt disease progression. The fruit extract of *Elaeagnus angustifolia* (EL) contains anti-inflammatory and antioxidant phytochemicals, including flavonoids, which may inhibit pro-inflammatory cytokines and oxidative stress. This randomized, double-blind clinical trial evaluated whether a standardized topical EL gel, as an adjunct to diclofenac, could reduce pain and stiffness and improve function in knee osteoarthritis.

Materials & Methods: In this randomized clinical trial, 112 patients aged 40 to 75 years with grade II–III osteoarthritis received diclofenac (25 mg, twice daily) for 8 weeks. The intervention group additionally applied EL fruit gel, while the control group used a placebo gel. Outcomes were evaluated at baseline, 4 weeks, and 8 weeks using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC).

Results: The mean differences in osteoarthritis symptoms and daily activity in the intervention group after 8 weeks showed significant improvements ($P < 0.001$) compared to baseline, with changes of 1.19 ± 0.17 and 2.50 ± 2.16, respectively. Additionally, significant reductions in stiffness ($P = 0.03$) and pain symptoms ($P = 0.03$) were observed in the intervention group compared to the placebo group, with changes of -0.69 ± 0.32 and -2.71 ± 1.26, respectively.

Conclusion: Topical EL fruit extract gel significantly reduced pain and stiffness compared to placebo. Its favorable safety profile supports the need for further large-scale trials to confirm efficacy and evaluate long-term safety.

Keywords: Osteoarthritis, Elaeagnus angustifolia, Knee Joint, Persian Medicine, Herbal Medicine

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1. Introduction

Osteoarthritis (OA) is the most common cause of arthritis, leading to joint pain, disability, and functional limitations in older adults (1). It is a characterized as a degenerative joint disease with inflammatory features based on radiological findings. Meanwhile, many molecular and biochemical findings suggest the inflammatory mechanisms for this disease (1, 2). OA can affect multiple joints, including the hands, hips, and knees. A major risk factor for OA is having a high body mass index (BMI), which is linked to excess weight.

In addition to weight, several factors such as age, gender, and genetic predisposition also play a role in the risk of developing this condition (3). Various studies conducted throughout the world reported that 595 million people had arthritis in 2020, which is equal to 7.6% of the world's population. This shows an increase of 132.2% compared with the 1990s. Compared to 2020, the number of individuals with OA is projected to grow by 9.74% for knee, 6.48% for hand, 6.78% for hip, and 1.95% for other body parts by 2050 (4).

In the pathogenesis of OA, there is a disturbed cytokine balance in favor of proinflammatory cytokines. An increase in the serum levels of cytokines such as tumor necrosis factor-alpha (TNF-α) and interferon-gamma (IFN-γ), activation of joint destructive enzymes such as matrix metalloproteinases (MMPs), and an increase in the serum levels of C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) have also been observed (5).

Treatment options for OA vary based on the severity and extent of the condition. Patients may receive treatment such as oral acetaminophen, topical ointments, non-steroidal anti-inflammatory drugs (NSAIDs) such as diclofenac, intra-articular corticosteroid injections, and, in severe cases, joint replacement surgery (6). However, most treatments for OA primarily focus on relieving pain and symptoms, and they do not halt the progression of the disease. Furthermore, no approved disease-modifying treatment for OA currently exists (7).

Persian Medicine and other traditional systems have long utilized plant-based remedies for chronic musculoskeletal conditions. *Elaeagnus angustifolia* L., known for its analgesic and anti-inflammatory properties, has been traditionally administered for the alleviation of joint pain. Phytochemical studies reveal that EL fruit contains flavonoids, phenolic acids, and other bioactive compounds with antioxidant and anti-inflammatory potential. These compounds may exert their effects through the inhibition of COX enzymes, suppression of pro-inflammatory cytokines, and modulation of oxidative stress (8).

The EL plant belongs to the *Elaeagnus* genus (Elaeagnaceae) and grows extensively in vast regions from North Asia to the Himalayas and Europe (9). In Persian Medicine, the extract of the *Elaeagnus* plant is well-known for its analgesic effects, and is traditionally used for relieving joint pain, though its specific anti-inflammatory properties may not be explicitly mentioned in classical sources. The decoction and infusion of its fruit are considered effective remedies for rheumatoid arthritis (10, 11).

In addition to the anti-inflammatory and joint pain-reducing effects of EL extract, recent studies have focused on further investigating these characteristics. A clinical trial involving 50 patients with mild to moderate knee osteoarthritis compared the therapeutic effects of EL (250 mg Elartrit capsules) and curcumin (370 mg capsules) taken orally every 12 hours for 15 days. Pain and function were assessed using the Visual Analogue Scale (VAS), Knee Injury and Osteoarthritis Outcome Score (KOOS), and Roles and Maudsley Scale before, 2 weeks, and 4 weeks after treatment. Both treatments significantly improved joint stiffness, pain, daily activity, and KOOS total scores compared to baseline, with no significant differences between the two groups in knee discomfort, joint stiffness, pain, daily activity, exercise, recreation, quality of life, or functional status after 4 weeks (12). A clinical trial investigated the efficacy of an aqueous extract of EA, containing 0.21% w/w kaempferol in comparison to ibuprofen in 97 patients with knee OA over a period of 7 weeks. Patients received either 300 mg/day (n=33) or 600 mg/day (n=32) of EA extract or 800 mg/day ibuprofen (n=32). Disease severity was assessed using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), VAS for pain, Lequesne's Pain-Function Index (LPFI), and Patient's Global Assessment (PGA) index. All three interventions significantly reduced WOMAC, VAS, LPFI, and PGA scores by the end of the trial, with no significant differences in efficacy between EA (low or high dose) and ibuprofen or between the two EA doses. EA was well-tolerated with no reported adverse events (13). In addition, a review study mentioned some of the properties and uses of EL fruit in Persian Medicine, including antioxidant activity, along with antinociceptive and anti-inflammatory effects, in the treatment of osteoarthritis (14).

Despite these promising effects of oral EL extract, topical formulations have not yet been systematically evaluated in knee OA. A topical delivery route may offer targeted drug exposure at the affected joint, minimize systemic side effects, and enhance patient adherence, yet no randomized trial has examined this approach in detail. Addressing this gap is important for translating traditional remedies into modern, accessible therapeutic forms.

Therefore, the present double-blind randomized controlled trial aims to evaluate the efficacy and safety of a standardized 10% extract gel from *Elaeagnus angustifolia* fruit as an adjunct to oral diclofenac in improving pain, stiffness, and physical function in patients with knee OA. This study hypothesizes that the topical application of EL gel, a traditional remedy adapted

for modern clinical use, may enhance OA symptom relief when used alongside standard care.

2. Materials and Methods

2.1 Plant Preparation

The *Elaeagnus angustifolia* fruit used in this study was collected in September 2023 from Varzaghan City, located in East Azerbaijan province in Iran. It received Voucher Specimen No: SBMU1052 from the Herbarium Center, Faculty of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

2.2 Extraction

The extraction from 100 g of fruit was performed using the following method: First, the fruits were washed and dried in the shade at room temperature. Then, 100 g of whole EL fruit without seed was boiled with 1000 ml of distilled water (DW) for 30 minutes. After 30 minutes, it was filtered using filter paper. The mixture was concentrated on a Bain-Marie at 90°C for 2 days to obtain its dry extract. Finally, 30 g of dry extract was obtained from every 100 grams of the EL fruit.

2.3 Drug and Placebo Formulation Design

The formulation of a 10% *Elaeagnus angustifolia* gel with a pH of 5 contains carbomer 934 powder, glycerin, 0.1 mol soda, 96% ethanol, distilled water, and EL fruit extract. First, the carbomer powder was weighed. Distilled water was then added, and a uniform mixture was achieved using an electric mixer. To create the desired 10% gel, glycerin, ethanol, 0.1 mol sodium hydroxide, and EL extract were incorporated. Finally, the gel was packaged in 100-gram tubes, stored at temperatures between 2°C and 3°C, and prescribed to patients. For the placebo formulation, carbomer 934 powder, glycerin, sodium carbonate, 96% ethanol, distilled water, and a natural dye were used. The placebo was then dispensed to patients in 100-gram tubes.

2.4 Determination of Total Phenolic Contents

To perform this stage of the study, Folin-Ciocalteu solution was used as a reagent, and gallic acid was utilized as a standard phenolic compound for measurements. For this purpose, 1 ml of gallic acid solution at different dilutions (10, 20, 40, 80, and 160 µg/ml) was mixed with 5 ml of Folin-Ciocalteau reagent diluted in a ratio of 1 to 10 and incubated at room temperature. After 10 minutes, 4 ml of 7.5 mg/ml sodium carbonate solution was added to the mixture. The final preparation was then incubated for 30 minutes at room temperature, protected from light. Then, the absorbance of each sample of gallic acid was measured at a wavelength of 765 nm. This experiment was conducted three times for each dilution of gallic acid. Based on the resulting absorbance data, a linear curve was created to represent the absorption of gallic acid versus concentration. The same method was also performed for the ELA product, and the total phenolic content was calculated using the gallic acid standard curve.

2.5 Standardization of ELA Aqueous Extract based on Kaempferol

Instrumentation and Analytical Procedures: The standardization used high-performance liquid chromatography (HPLC). The ELA extract was obtained by boiling the fruit, revealing a water content of approximately 20.3%. The hydrolysis was conducted by adding 25% hydrochloric acid to the mixture and maintaining the temperature at 83 °C for a duration of 45 minutes. After hydrolysis, methanol was used to dissolve the kaempferol. For chromatographic analysis, the mobile phase consisted of methanol (1:10:30:60) adjusted to pH 4, along with distilled water, acetonitrile, and phosphoric acid, at a flow rate of 4.1 mL/min and a maximum absorption wavelength of 365 nm using an RP C18 column. A calibration curve was created using various concentrations of kaempferol (0.25, 0.41, 0.6, 0.8, 1.1, 1.65, and 2 ng/mL in methanol), with triplicate measurements for accuracy.

2.6 Patient Selection

This study was conducted based on a sample size calculation and the outcome measures reported by Panahi et al **(13)**. Considering a confidence level of 0.95 and a power of 0.80 (including α=0.05 and β=0.2), in this randomized controlled trial, at least 51 people in each group were required. It means the total sample size needed was 102 people. However, to account for a 10% probability of sample dropout during the study, the total sample size was adjusted to 112 participants. Therefore, the sample size in each group would be 56 people.

2.7 Inclusion Criteria

A rheumatologist diagnosed patients with osteoarthritis (OA) through a combination of patient history, clinical examination, and knee radiography. Consequently, the clinical evidence for early knee osteoarthritis (OA) was established in accordance with the guidelines set by the American College of Rheumatology (ACR) **(15)**. Patients were enrolled after providing informed consent if their knee pain was aggravated by activity, relieved by rest, and accompanied by morning stiffness lasting less than 30 minutes. Accordingly, the inclusion criteria for this study comprised documented informed consent, age between 40 and 75 years, non-traumatic knee pain persisting for more than 6 months (with activity-related aggravation and relief by rest), morning stiffness of less than 30 minutes, and a diagnosis of osteoarthritis based on the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) **(16)**, plus the Kellgren/Lawrence (K/L) scale, a widely accepted grading system that evaluates osteoarthritis severity based on joint space narrowing, osteophyte formation, subchondral sclerosis, and bone deformity **(17)**, and knee radiography ratings from the past 6 months.

2.8 Exclusion Criteria

Exclusion criteria included hip osteoarthritis, septic arthritis, active gastrointestinal bleeding, previous joint surgery, a body mass index (BMI) exceeding 30, diabetes,

rheumatism, osteonecrosis and gout, history of stomach or duodenal ulcers, blood pressure above 140/90, allergy to diclofenac and EL extract, history of heart attack in the past 12 months, concurrent use of furosemide, probenecid, anticoagulants, hydantoin, sulfonamides, lithium salts, methotrexate, β-blockers, and muscle relaxants, history of corticosteroid use in the past 4 months, and during pregnancy or breastfeeding, and unwillingness to continue participation in the study.

2.9 Study Design

A rheumatologist confirmed the diagnosis of osteoarthritis after a thorough examination and knee radiographs. One of the main inclusion criteria was the analysis of X-ray images of the joints to diagnose osteoarthritis, the degree of joint space narrowing, and the degree of sclerosis (grade II) or osteophyte formation (grade III) in the joint (17). The patient was referred to the researcher after obtaining informed consent, where the researcher explained the treatment protocol in detail. The prescribed drug was used twice a day (in the morning and at night) in both groups for eight weeks. The intervention group received treatment with diclofenac 25 mg tablets plus 10% *Elaeagnus angustifolia* gel, while the placebo group received diclofenac 25 mg tablets plus a placebo gel. The gel in both groups was applied as a fingertip unit (2.5 g) by rubbing or covering the affected knee in a clockwise direction without performing an actual massage. Participants were advised to wash their hands and knees before the application of the gel. The WOMAC questionnaire was completed before intervention, as well as after 4 and 8 weeks after the intervention.

2.10 Safety Assessment

The patient was provided with the project manager's phone number for questions throughout the treatment. Each visit included a form to track medication side effects and follow-ups. Weekly phone calls focused on medication adherence, treatment effects, and side effects. Medications were delivered in person the day before the intervention and on day 28. A rheumatologist visited the patient during the medication delivery and after the treatment course, with all information documented in the patient's file.

2.11 Randomization and Blinding

A randomized block design was used to randomize patients. For this purpose, 112 envelope were allocated in blocks of 4, between the two intervention and placebo groups. In this process, diclofenac tablets were administered concurrently, and the tubes containing the EL gel and the placebo gel were indistinguishable in appearance. The researcher and participants were unaware of the group assignments for the ointment and placebo, with only the pharmaceutical consultant having this knowledge.

2.12 Outcome Measures

In this study, the WOMAC questionnaire was used to evaluate the effectiveness of the intervention. This questionnaire is considered one of the most reliable international tools for patients with osteoarthritis. The validity and reliability of its Persian version were introduced by Ebrahimzadeh et al (16) in 2014. This questionnaire has three sections: pain, joint stiffness, and physical function (health and function). It includes a total of 33 question items covering clinical symptoms (5 questions), severity of joint stiffness (2 questions), pain level (9 questions), and daily living activities (17 questions). Each question has 5 options, with the first option receiving a response of never or none, and the fifth option receiving a response of extreme. Note that patients completed the questionnaire before the intervention, as well as at 4 and 8 weeks post-intervention.

2.13 Statistical Analysis

Data analysis was conducted utilizing SPSS (Statistical Package for the Social Sciences) software, version 19. The assessment of normality for quantitative variables was performed through the Shapiro–Wilk test. Demographic variables were reported as counts and percentages, along with their statistical significance. Comparisons of quantitative variables were conducted using the independent t-test, while qualitative variables were analyzed using the Chi-square or Fisher's exact test, as applicable. Statistical tests consisting of analysis of variance (ANOVA) and repeated measures were employed to evaluate the results. In addition, descriptive statistics included mean, standard deviation, and mean difference. Comparison between the groups before and after the intervention was performed using the independent samples t-test (or a non-parametric equivalence test, i.e., the Mann–Whitney U test) and the paired samples t-test (or a non-parametric equivalence test, i.e., the Wilcoxon test). A p-value of less than .05 was considered statistically significant.

3. Result

Elaeagnus angustifolia is a rich source of flavonoids and other phytochemicals with potent antioxidant, anti-inflammatory, antimicrobial, and protective properties. These bioactive compounds underline their considerable therapeutic potential in both traditional and modern medicine. The standardized aqueous extract of *Elaeagnus angustifolia* fruit contains 3.7% total phenols per 100 grams (Table 1).

The kaempferol content of the aqueous extract of *Elaeagnus angustifolia*, measured by HPLC, was found to be 0.21% per 100 g (Figure 1).

In this randomized controlled trial, we recruited 112 patients with knee osteoarthritis from an initial pool of 200 screened individuals. Of these, 80 were excluded for not meeting inclusion criteria or for unwillingness to participate, and 8 were removed during the intervention for unknown reasons, as shown in Figure 2. Notably, there were no reported side effects related to either the drug or the placebo throughout the duration of the study.

Table 2 presents the baseline characteristics of the study participants in the intervention (Group A) and placebo

(Group B) groups. It includes several variables such as age, BMI, sex, education level, knee side (right or left), and degree of radiographic severity. The mean age and BMI were comparable between the two groups, with no statistically significant differences ($p > 0.05$). Overall, the baseline characteristics of participants in both groups were comparable, and the study design effectively controlled for these baseline differences, thereby minimizing potential confounding factors.

Table 3 presents the mean WOMAC Scores and standard deviations (SD) for both the intervention and placebo groups at three time points: T1 (pre-intervention), T2 (post-4 weeks), and T3 (post-8 weeks). The table includes various symptom categories, such as symptoms, stiffness, pain, and daily activities. The intervention group exhibited a significant reduction in WOMAC symptom scores over time, with statistically significant improvements observed for all pairwise comparisons (T1 vs. T2, T1 vs. T3, and T2 vs. T3; all $p<0.001$). Similarly, the placebo group showed a significant reduction in symptoms over time ($p<0.001$) for all pairwise comparisons. However, the mean difference between the intervention and placebo groups at each time point was not statistically significant (Table 3, Figure 3).

Both intervention and placebo groups demonstrated a significant fall in stiffness over time (p-values<0.001 for all pairwise comparisons). The mean difference between groups at each time point, T1 and T2, was not statistically significant (P=0.07). At time point T3, the intervention group demonstrated a significantly lower stiffness score compared to the placebo group (P=0.03) (Table 3), reflecting a greater improvement in joint stiffness.

Both intervention and placebo groups experienced a significant decline in pain over time ($p<0.001$ for all pairwise comparisons). Notably, there was a statistically significant difference between the groups at time point 3, with the placebo group showing higher pain scores compared to the intervention group (P=0.03) (Table 3).

The intervention group indicated a significant improvement in daily activity over time ($p<0.001$ for all pairwise comparisons). Similarly, the placebo group also demonstrated a significant improvement in daily activity ($p<0.001$ for all pairwise comparisons). The mean difference between groups at each time point was not statistically significant (Table 3).

Table 1. Determination of total phenolic content in the ELA product using the Folin-Ciocalteu method and gallic acid standard curve.

Herbal product	Concentration	Total phenolic/Gallic acid (ug/ml)	Total phenol
ELA product	1.2 mg/ml	44.4	3.7%

Table 2. The baseline characteristics of the study participants.

		Treatment group	Placebo group	Total	P-value
	Age (year) (Mean± SD)	58.02 ± 11.10	59.50 ± 8.80	58.76 ± 10.00	0.435*
	BMI (Mean± SD)	26.49 ± 2.72	26.54 ± 2.69	26.59 ± 2.69	0.855*
	Sex (Male) N (%)	8 (14.3%)	10 (17.9%)	18 (16.1%)	0.607**
Education Level N (%)	Illiterate	28(50%)	26 (46.4%)	54 (48.2%)	0.900***
	Under diploma	20 (35.7%)	19 (33.9%)	39 (34.8%)	
	Diploma	6 (10.7%)	8 (14.3%)	14 (12.5%)	
	Higher Education	2 (3.6%)	3 (5.4%)	5 (4.5%)	
Direction of the Knee N (%)	Right	6 (10.7%)	7 (12.5%)	13 (11.6%)	0.940***
	Left	13 (23.2%)	12 (21.4%)	25 (22.3%)	
	Right & Left	37 (66.1%)	37 (66.1%)	74 (66.1%)	
Degree of Radiography N (%)	II (%)	15 (26.8%)	9 (16.1%)	24 (21.4%)	0.383***
	II & III (%)	10 (17.9%)	11 (19.6%)	21 (18.8%)	
	III (%)	31 (55.4%)	36 (64.3%)	67 (59.8%)	

* Independent samples t-test, ** Chi-squared test, *** One-way ANOVA.

Table 3. Repeated measures analysis of WOMAC subscale scores (symptoms, stiffness, pain, and daily activity) in intervention and placebo groups.

Variable	Group	T1	T2	T3	*P-value**	T1 vs T2 (Mean difference ± SE)* Percentage change	T1 vs T3 (Mean difference ± SE)* Percentage change	T2 vs T3 (Mean difference ± SE) Percentage change
Symptoms	Group A (Mean ± SD)	8.33 ± 3.60	5.94 ± 3.11	4.75 ± 3.10	**<0.001**	2.39 ± 0.22 -28.69%	3.58 ± 0.29 -42.98%	1.19 ± 0.17 -20.03%
	Group B (Mean ± SD)	8.57 ± 3.8	6.53 ± 3.6	5.78 ± 3.66	**<0.001**	2.03 ± 0.24 -23.80%	2.78 ± 0.33 -32.56%	0.75 ± 0.13 -11.49%
	Mean Difference	-0.23 ± 0.70	-0.58 ± 0.64	-1.03 ± 0.64				
	Cohen's d	-0.06	-0.18	-0.30				
	*P-value***	0.74	0.36	0.106				
Stiffness	Group A (Mean ± SD)	3.16 ± 2.34	2.14 ± 1.69	1.69 ± 1.45	**<0.001**	1.01± 0.15 -32.28%	1.46 ± 0.21 -46.52%	0.44 ± 0.11 -21.03%
	Group B (Mean ± SD)	3.62 ± 2.30	2.76 ± 1.99	2.39 ± 1.92	**<0.001**	0.85 ± 0.15 -23.76%	1.23 ± 0.21 -33.98%	0.37 ± 0.11 -13.41%
	Mean Difference	-0.46 ± 0.43	-0.62 ± 0.35	-0.69 ± 0.32				
	Cohen's d	-0.20	-0.34	-0.41				
	*P-value***	0.29	0.07	**0.03**				
Pain	Group A (Mean ± SD)	19.46 ± 6.51	14.28 ± 5.50	11.51±5 .64	**<0.001**	5.17 ± 0.47 -26.62%	7.94 ± 0.72 -40.85%	2.76 ± 0.38 -19.40%
	Group B (Mean ± SD)	20.00 ± 6.48	15.60 ± 6.94	14.23 ± 7.63	**<0.001**	4.39 ± 0.46 -22.00%	5.76 ± 0.71 -28.85%	1.37 ± 0.46 -8.78%
	Mean Difference	-0.53 ± 1.22	-1.32 ± 1.18	-2.71 ± 1.26				
	Cohen's d	-0.08	-0.21	-0.41				
	P-value**	0.66	0.26	**0.03**				
Daily Activity	Group A (Mean ± SD)	31.07 ± 13.57	21.73 ± 10.51	19.23 ± 18.58	**<0.001**	9.33 ± 0.98 -30.06%	11.83 ± 2.41 -38.11%	2.50 ± 2.16 -11.50%
	Group B (Mean±SD)	29.73±13. 55	23.53±1 3.31	20.01±1 3.51	**<0.001**	6.19 ± 0.98 -20.85%	9.71 ± 1.38 -32.69%	3.51 ± 0.76 -14.96%
	Mean Difference	1.33±2.56	- 1.80±2. 26	- 0.78±3. 07				
	Cohen's d	+0.10	-0.15	-0.05				
	P-value**	0.60	0.42	0.79				

*. P<0.001, adjusted for multiple comparisons using Bonferroni. **. *P-value*, between groups, * *P-value*, within groups, T1 (before intervention), T2 (after 4 weeks), T3 (after 8 weeks), Group A (intervention), Group B (placebo)

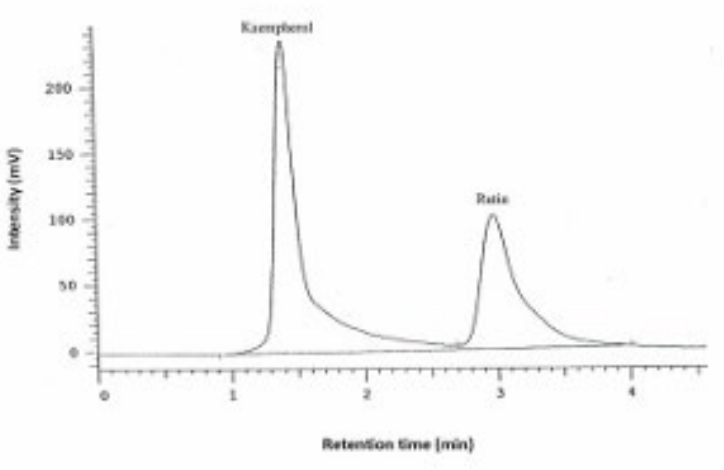


Figure 1. HPLC determination of kaempferol content in the *Elaeagnus angustifolia* extract. Rutin was used as the internal standard (**Prepared by Authors, 2025**).

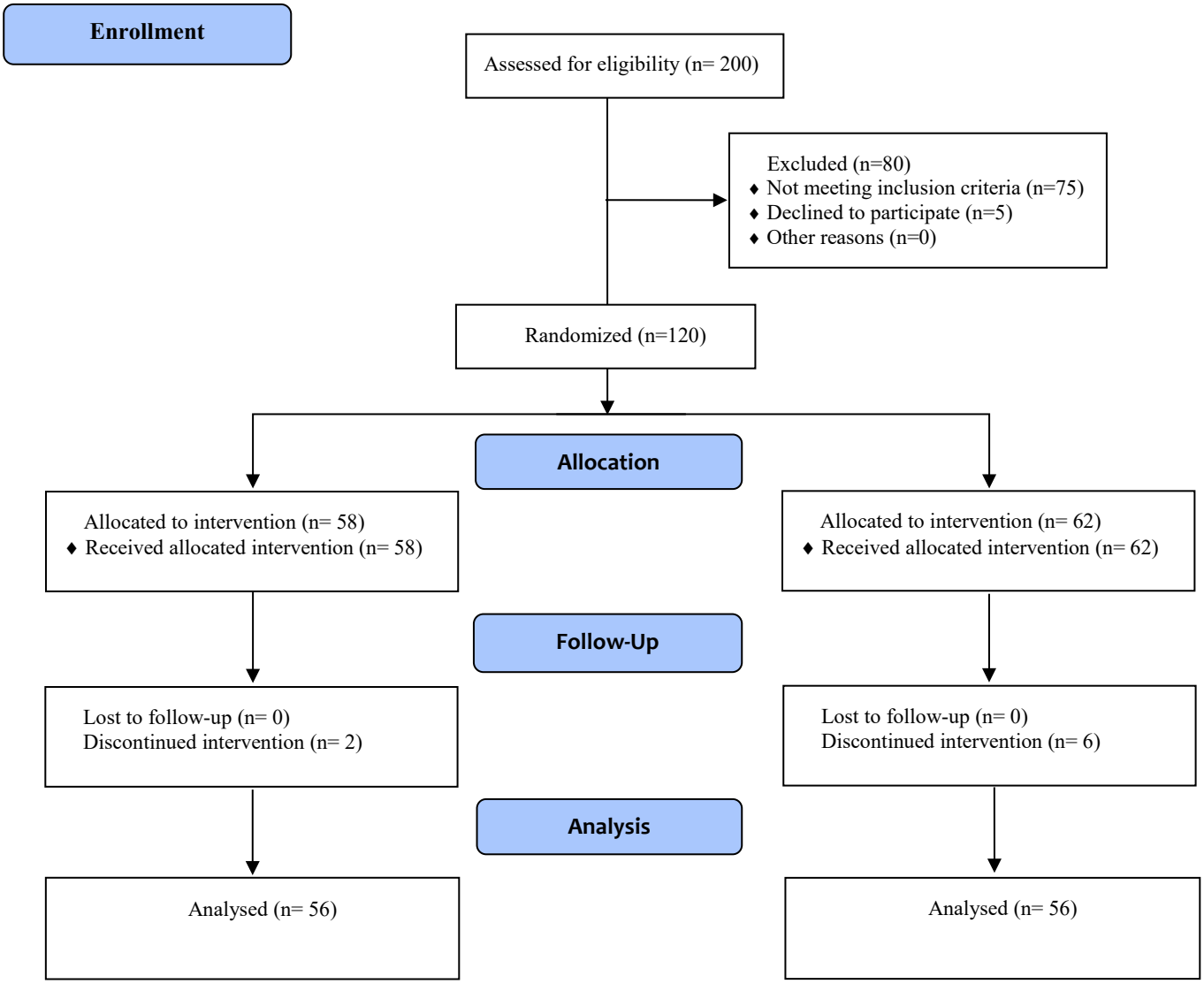


Figure 2. The CONSORT flowchart of the study (**Prepared by Authors, 2025**).

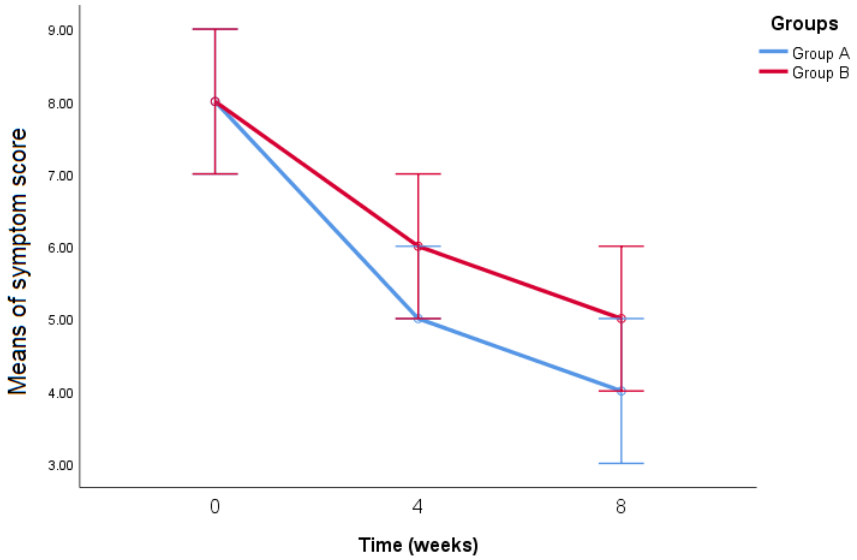


Figure 3. Comparison of longitudinal changes in knee osteoarthritis symptoms (Pain, Stiffness, and Daily Activity) over 8 weeks (WOMAC Subscales) in the intervention (Group A) vs. placebo (Group B) groups (**Prepared by Authors, 2025**).

4. Discussion

In this double-blind, placebo-controlled trial, we found that topical *Elaeagnus angustifolia* fruit extract gel significantly improved pain, stiffness, and physical function in patients with knee osteoarthritis (OA). This is the first clinical study to evaluate a topical EL gel formulation for OA symptoms, thereby extending the evidence base for EL beyond its oral administration and non-musculoskeletal applications.

In terms of specific outcomes, both intervention and placebo groups demonstrated significant reductions in stiffness and pain over time, suggesting that non-specific factors such as the placebo effect and standard care may contribute to symptom improvement. However, a clearer treatment effect of EL gel emerged at later time points. At week 8 (T3), the intervention group showed significantly greater reductions in stiffness (P=0.03) and pain (P=0.03) compared to The placebo group also showed improvements, suggesting that the benefits of EL gel may become more pronounced with continued use. While daily activity scores improved significantly in both groups, no significant differences were observed between them. This lack of distinction may reflect the multifactorial nature of functional outcomes in osteoarthritis (OA). Together, these findings suggest that EL gel offers incremental benefits beyond placebo, particularly for pain and stiffness, though larger trials with longer follow-up are needed to confirm the durability and clinical relevance of these effects.

Our findings build on previous evidence in two ways. First, they demonstrate that topical application—at a higher concentration (10%) than typically tested in oral formulations—can produce meaningful symptom relief. Second, they highlight the potential of EL gel as a safe and non-invasive add-on therapy for OA management.

When contextualized within the literature, these results are consistent with earlier research on EL and other herbal interventions for OA. Topical applications of EL have previously been explored in dermatology, with Salamzadeh et al **(18)** demonstrating the efficacy of EL gel in alleviating radiotherapy-induced skin inflammation and discomfort.

Oral EL trials in OA also support our findings. For example, studies by Ebrahimi et al **(19)**, Karimifar et al **(20)**, Panahi et al **(13)**, and Vahdatpour et al **(12)** demonstrated reductions in pain and improvements in WOMAC scores, with EL showing comparable effects to conventional drugs such as ibuprofen and curcumin. Meta-evidence suggests that EL exerts its therapeutic benefit through anti-inflammatory and antioxidant mechanisms, including inhibition of COX-1/COX-2, downregulation of TNF-α and MMP enzymes, and upregulation of IL-10 and antioxidant activity **(21-23)**. Rather than a single effective dose, studies examining a range of oral doses (200–600 mg of extract or 15 g of fruit/powder) consistently report a reduction in symptoms, thereby supporting a robust therapeutic signal.

Comparative herbal interventions provide additional context. Khamevar et al **(24)** reported improved WOMAC scores with *Pistacia atlantica* ointment, while Naderi et al **(25)** demonstrated pain reduction with ginger powder. These parallels emphasize the broader potential of plant-based therapies as complementary treatments for osteoarthritis (OA).

Preclinical evidence reinforces the analgesic and chondroprotective potential of EL. Animal studies by Ahmadiani et al **(10)**, Tamtaji et al **(26)**, and Nasrabadi et al **(27)** have shown reductions in pain, MMP activity, and cartilage degradation, aligning with our observed clinical benefits.

Taken together, our findings suggest that EL gel may represent a novel, locally acting option for OA

management, complementing both oral phytotherapeutics and standard pharmacological therapies.

These findings warrant further exploration of EL gel in larger, multicenter trials with longer follow-up and mechanistic evaluations to confirm efficacy and safety.

5. Conclusion

In conclusion, topical *Elaeagnus angustifolia* extract gel demonstrated meaningful clinical potential in managing knee osteoarthritis symptoms. Both the intervention and placebo groups demonstrated significant improvements in pain, stiffness, and daily activity over time, highlighting the effects of the placebo response as well as natural variability in the disease. However, by week 8, the intervention group exhibited significantly greater reductions in stiffness and pain compared to placebo, suggesting that the benefits of EL gel may emerge more clearly with sustained use. Improvements in daily activity were observed in both groups without between-group differences. While within-group changes were significant, between-group differences at earlier time points did not reach statistical significance, underscoring the need for cautious interpretation. Larger trials with extended follow-up are required to clarify the clinical relevance of these findings. Future research should also investigate mechanistic pathways by evaluating serum biomarkers such as TNF-α, IL-6, and MMP enzymes. If confirmed, EL gel could provide a safe, accessible, and non-invasive complementary option in the management of knee osteoarthritis.

6. Declarations

6.1 Acknowledgments

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6.2 Ethical Considerations

This double-blind randomized clinical trial was conducted on patients referring to Sayad Shirazi Hospital in Gorgan, Golestan province, Iran, from 2023 to 2024. This study was approved by the Ethics Committee of Tehran University of Medical Sciences (IR.TUMS.SPH.REC.1400.011). Patient confidentiality was maintained through anonymization of identifiers during data extraction. Written informed consent was obtained from all patients, and all steps of the study were in accordance with the Helsinki declaration.

6.3 Authors' Contributions

H. Alipour: Designed the study, obtained informed consent, collected data, and drafted the manuscript. M. Qaraaty: Supervised all stages of the study, edited, and approved the final manuscript. S. Sedighi: Confirmed the patients' osteoarthritis diagnoses and reviewed the manuscript. A. Rajabi: Randomized patients and analyzed the data. M. Kamalinejad: Prepared Elaeagnus angustifolia and its gel, as well as the placebo, and wrote the herbal specifications.

6.4 Conflict of Interest

The authors declare that they have no conflict of interest. They take full responsibility for the accuracy and integrity of the content of this paper.

6.5 Fund or Financial Support

This research did not receive any financial support from public or private funding agencies.

6.6 Using Artificial Intelligence Tools (AI Tools)

The authors were not utilized AI Tools.

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