

Original Article



Efficacy of Topical *Saussurea lappa* Oil for Knee Osteoarthritis: A Randomized Controlled Trial

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Article History:

Received: September 1, 2025

Revised: October 5, 2025

Accepted: October 15, 2025

ePublished: March 1, 2026

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Abstract

Objectives: *Saussurea lappa* oil is an herbal remedy used in traditional medicine for joint pain. In this study, *S. lappa* oil was specifically tested as a topical treatment for knee osteoarthritis (OA).

Design: A Randomized Controlled Trial.

Setting(s): Tabriz University of Medical Sciences, Shohada Hospital.

Participants: Older adult patients.

Methods: Older adult patients hospitalized with knee osteoarthritis were randomly assigned to two trial arms. For 4 weeks, participants applied either *S. lappa* oil or placebo (paraffin oil) topically twice daily. Knee pain was assessed using the visual analogue scale (VAS), and physical function was evaluated using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and knee flexion angle at baseline and at weeks 2 and 4.

Outcome Measures: Satisfaction of older adults with hospital services.

Results: Based on the results, the *S. lappa* group demonstrated significant improvements in overall pain and physical function, with reductions in the global and subscale WOMAC scores, while the placebo group showed no improvement in most outcomes, except for a significant decrease in stiffness. Between-group analyses favored *S. lappa* over placebo, particularly for reducing global pain and physical function. Similarly, VAS pain scores substantially decreased in the *S. lappa* group, with no marked change in the control group.

Conclusions: *S. lappa* revealed short-term improvements in pain and functional mobility (notably VAS, WOMAC, and the 8-m walk at 2 weeks) and was associated with reduced analgesic use and no reported adverse events. Nonetheless, the benefits were not consistently statistically significant versus the placebo and the study's limited sample size and follow-up constrain confidence, indicating the need for larger, longer, and more rigorous trials to confirm its efficacy and safety.

Keywords: Knee osteoarthritis, *Saussurea lappa*, *Alpinia officinerum* Hance, Bitter costus, Indian Costus, Complementary medicine, Traditional Persian Medicine

Please cite this article as follows: Mirahmadi M, Sadeghpour Teymurloui A, Fazljou SMB, Araj Khodaei SM, Najjarsadeghi S, Bagherzadeh Karimi A et al. Efficacy of topical *Saussurea lappa* oil for knee osteoarthritis: a randomized controlled trial. Int J Aging 2026;4:e9149. doi:10.34172/ija.9149

Introduction

Osteoarthritis (OA) is a prevalent degenerative joint disease primarily affecting older adults.^{1,2} It is characterized by several features, including the erosion of joint cartilage, hypertrophy of adjacent bones (osteophytes), sclerosis of the subchondral bone plate, and a variety of chemical and morphological changes in the synovial membrane and joint capsule.^{1,2} As the most common form of arthritis, OA poses a significant public health challenge, particularly due to its high prevalence among the elderly and the associated

disability it causes.^{3,4} Moreover, the increasing aging population and rising obesity rates are contributing to a growing incidence of OA, making it a leading cause of disability in older adults.^{3,4} Globally, OA ranks as the fifth leading cause of years lost due to disability in high-income countries and the ninth in middle-income and low-income countries.^{5,6} It is estimated that radiographic signs of knee OA (KOA) are present in approximately 30% of individuals over the age of 65. Furthermore, some studies suggest that 9.6% of men and 18% of women over 60 years old experience



symptomatic OA.^{5,6} Among these individuals, nearly 80% face mobility limitations, and 25% are unable to perform essential daily activities. In addition, this high prevalence is accompanied by a substantial economic burden, highlighting the need for effective management strategies.⁷ The prevalence of KOA is reported to be 15.3% and 19.3% in the urban and rural regions of Iran, respectively. With regard to years lost due to disability, KOA ranks seventh in Iran, following lower back pain.^{8,9} A study conducted on the burden of diseases and injuries in Iran identified KOA as the ninth leading condition in terms of disease burden, trailing behind other significant health issues, such as accidents, cardiovascular diseases, and mental health disorders.¹⁰ Clinically, OA presents with a range of symptoms, including pain, stiffness, joint deformity (bowing), and joint locking, especially during flexion.^{11,12} Likewise, inflammatory arthritis and bursitis may occur in chronic cases. The primary treatment goals for OA are to alleviate pain, minimize the loss of physical function, and reduce inflammation, weakness, and joint instability.^{11,12} Furthermore, current therapeutic approaches for OA encompass both non-pharmacological and pharmacological treatments. Additionally, acetaminophen, oral and topical nonsteroidal anti-inflammatory drugs (NSAIDs), oral cyclooxygenase-2 (COX-2) inhibitors, and opioids are among the most commonly used pharmacological options for OA.^{13,14} While acetaminophen is widely used, it can increase the half-life of warfarin and has potential hepatotoxic effects. Similarly, oral and topical NSAIDs, which inhibit COX-1 and COX-2 enzymes, are associated with various side effects, including cardiovascular events and gastrointestinal and renal complications.^{13,14} Although topical NSAIDs tend to have fewer systemic side effects than their oral counterparts, concerns about their safety remain. Given the increasing reliance on NSAIDs and the growing reports of their adverse effects, there is a pressing need to explore alternative therapeutic options,¹⁵ including the scientific investigation of medicinal plants that may offer similar anti-inflammatory and analgesic effects with fewer side effects.¹⁶ Therefore, this study aims to evaluate the efficacy of the *Saussurea lappa* oil as a topical treatment for KOA, comparing its effects to those of a placebo.¹⁶ By exploring the potential benefits of this herbal remedy, the study seeks to contribute to the development of safer and more effective treatment strategies for individuals suffering from OA. Complementary and alternative medicine (CAM) therapies are generally accessible and widely utilized, particularly in low-income and middle-income countries.^{17,18} Moreover, many of these traditional remedies are supported by empirical evidence regarding their safety and efficacy, frequently derived from sources such as traditional medicine texts, pharmacopoeias, and clinical experiences accumulated over the years.^{19,20} An increasing number of scientific studies are now validating the use of certain CAM therapies, reflecting a growing interest in these approaches. In addition, one significant reason for the rising preference among patients for this approach is the increasing prevalence of chronic and

debilitating diseases for which conventional treatments may be inadequate or unavailable.^{19,20} The diversity, flexibility, and ease of access to CAM therapies have made them appealing options in many parts of the world. Their prevalent acceptance in low-income and middle-income countries, combined with relatively low costs and minimal technological requirements, positions CAM as a potential contributor to improving healthcare systems globally.^{21,22} However, further research is needed to enhance evidence-based practices regarding the impact of many CAM therapies. It is noteworthy that facilitating research activities in this field requires several measures, including the formal recognition of traditional, complementary, and alternative medicine, increased investment in research, the promotion of appropriate research methodologies for assessing specific CAM treatments, and the expansion of systems to protect their intellectual rights.^{21,22} Traditional medicine has long been integrated into the healthcare systems of various cultures, gaining acceptance among the populations it serves. This type of medicine offers unique advantages over imported medical systems, as it is deeply embedded in the cultural heritage of the people and plays a significant role in addressing certain health-related cultural issues. Furthermore, traditional medicine can effectively complement scientific and global medical practices, and its promotion and development reflect respect for the cultural and historical legacies of communities worldwide. The current study primarily aims to evaluate the efficacy and safety of the *S. lappa* oil as a topical treatment for KOA, comparing its effects to those of a placebo. By investigating the potential benefits of this traditional remedy, the study endeavors to contribute to the growing body of evidence supporting the use of CAM in managing chronic musculoskeletal conditions. Additionally, this research seeks to enhance understanding of the role of herbal therapies in contemporary healthcare, ultimately promoting a more integrative approach to patient care that respects cultural practices and addresses the needs of individuals suffering from OA. A distinctive feature of traditional medicine is its holistic approach, which considers the individual within a broad environmental context. Further, this perspective emphasizes that health and illness result from imbalances and disruptions within the entire system surrounding the individual. From this viewpoint, pathogenic factors and changes are perceived as secondary influences, highlighting the importance of maintaining equilibrium for overall well-being. As the interest in CAM continues to grow, it is crucial to explore and validate these traditional practices in order to ensure their safe and effective integration into modern healthcare systems.

The plant typically grows to a height of 1–2 m and features large, ovate leaves with a hairy texture. The flowers are typically white or pale yellow, arranged in a dense, terminal cluster.^{23,24} *S. lappa* is generally identified as Kushta or Indian Costus Root.^{25,26} This plant is native to the high-altitude regions of the Himalayas, including Kashmir and the Alpine ranges, and is also found in parts

of India, China, Korea, and Japan.²⁷

Historically, *S. lappa* has been revered in traditional medicine systems, particularly in Ayurveda, for its wide range of therapeutic properties. Moreover, *S. lappa* has been used for its hepatoprotective properties to protect the liver from damage caused by toxins and drugs.²⁸ Numerous studies have confirmed the efficacy of *S. lappa* in treating conditions such as rheumatoid arthritis (RA),²⁹ infectious diseases³⁰ treating leprosy,³¹ and fungal disease³² It also has motility inhibitory effects on helminths.³³ In addition, the plant's potent antioxidant properties contribute to its ability to protect against oxidative stress and related disorders such as cancer of human hepatoma cell line.³³

Previous studies have extensively investigated the chemical composition of *S. lappa*, identifying a variety of bioactive compounds. Specifically, some phytochemical studies have revealed that *S. lappa* contains a variety of bioactive compounds, including costunolide,³⁴ dehydrocostus lactone,³⁴ and alantolactone.³⁵ These sesquiterpene lactones are primarily responsible for the plant's anti-inflammatory, antimicrobial, and anticancer activities.³⁶ Research has also demonstrated that these compounds can inhibit the growth of various pathogens and cancer cells, emphasizing the potential of *S. lappa* as a source of novel therapeutic agents.³⁷ The roots of this plant are rich in essential oils and bioactive compounds, such as terpenoids, phenols, flavonoids, and acids, which contribute to its medicinal value. These compounds have been utilized for treating various ailments, including gastric ulcers, skin diseases, and menstrual disorders.³⁸ Further, the plant is commonly used as a remedy for digestive disorders,³⁹ respiratory ailments,³⁸ and inflammatory conditions.³⁹ Likewise, the roots of the plant are often included in herbal formulations in order to treat asthma and dysentery^{40,41} Furthermore, *S. lappa* contains flavonoids, lignans, triterpenes, steroids, glycosides, and alkaloids. These secondary metabolites contribute to the plant's diverse pharmacological activities, such as antioxidant, antimicrobial, and anti-ulcer effects.⁴²

The pharmacological study of intraperitoneal injection of the *S. lappa* extract for 20 days demonstrated the alleviation of OA-induced increase of inflammatory agents such as interleukin-6 (IL), tumor necrosis factor-alpha (TNF- α), and IL-1 β in mice serum.⁴³

Recent clinical studies have also indicated that *S. lappa* can reduce pain and swelling associated with OA; therefore, the topical application of the *S. lappa* oil was assessed for the treatment of KOA symptoms.

RA commonly occurs in people aged 25–55, and women are affected more often than men, at a ratio of about 3:1. Moreover, the condition is marked by synovial thickening, new blood vessel formation, and infiltration by mononuclear cells.

Inflammatory Markers

Serum concentrations of the cytokines IL-1 β , IL-6, and TNF- α were quantified using high-sensitivity, rat-specific quantitative sandwich immunoassay kits according to the manufacturers' protocols. The assays had a detection limit of 1 pg/mL. Serum C-reactive protein (CRP) levels were

measured using an immunoperoxidase-based sandwich ELISA kit, following the manufacturer's instructions. Figure 1 shows histological findings in the knee joint rats treated with 200 mg/kg *S. lappa*.

Methods

Study Design

This study was a randomized, double-blind, parallel-group, controlled clinical trial conducted in accordance with the Declaration of Helsinki and applicable Iranian regulations for clinical research. It is noteworthy that the trial protocol was approved by the Medical Ethics Committee of Tabriz University of Medical Sciences (No. IR.TBZMED.FMD.REC.1402.317). In addition, the study was registered in the Iranian Registry of Clinical Trials (clinical registration No. 20230909059389N1). Participants were also recruited from Tabriz Shohada Hospital between September 2024 and March 2025.

Participants

Eligible participants were adults aged 40–70 years with KOA of Kellgren–Lawrence grade 1–3. Moreover, diagnosis and eligibility were based on the Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and visual analogue scale (VAS) assessments, supported by knee clinical examination and knee radiography. After eligibility confirmation and written informed consent obtained from participants (or their legal guardians), participants were enrolled and allocated to one of the two study groups.

Eligibility Criteria

Participants were included if they had KOA diagnosed using WOMAC and VAS criteria, pain in at least one knee for the preceding 3 months, Kellgren–Lawrence grade 1–3 disease, and VAS pain rated as moderate to minimally bothersome at least 4 weeks before study entry.

However, they were excluded if they reported sensitivity or allergy to the *S. lappa* oil, had secondary OA (including RA, gout, infectious arthritis, metabolic arthritis, or traumatic arthritis), had undergone knee joint replacement surgery, or used oral or topical steroids within 14 days before the study. Likewise, they were excluded if they received intra-articular steroid injection within 90 days prior to the study, had chronic diseases (e.g., diabetes or cancer), had uncontrolled blood pressure, had a history of cerebral hemorrhage, were pregnant or breastfeeding, had addiction to alcohol or narcotic/psychotropic drugs, or had radiculopathy or neuropathy.

Randomization, Allocation Concealment, and Blinding

Following the baseline evaluation, participants were randomly allocated in a 1:1 ratio to group A or B using fixed-block randomization (block size = 4), which created 24 blocks in total. The randomization schedule was produced by a biostatistician with Microsoft Excel (2024). Further, allocation was concealed by using sequentially numbered, opaque, sealed envelopes prepared by the clinic secretary. Each envelope contained the group assignment letter (A or B), corresponding to the active treatment or placebo.

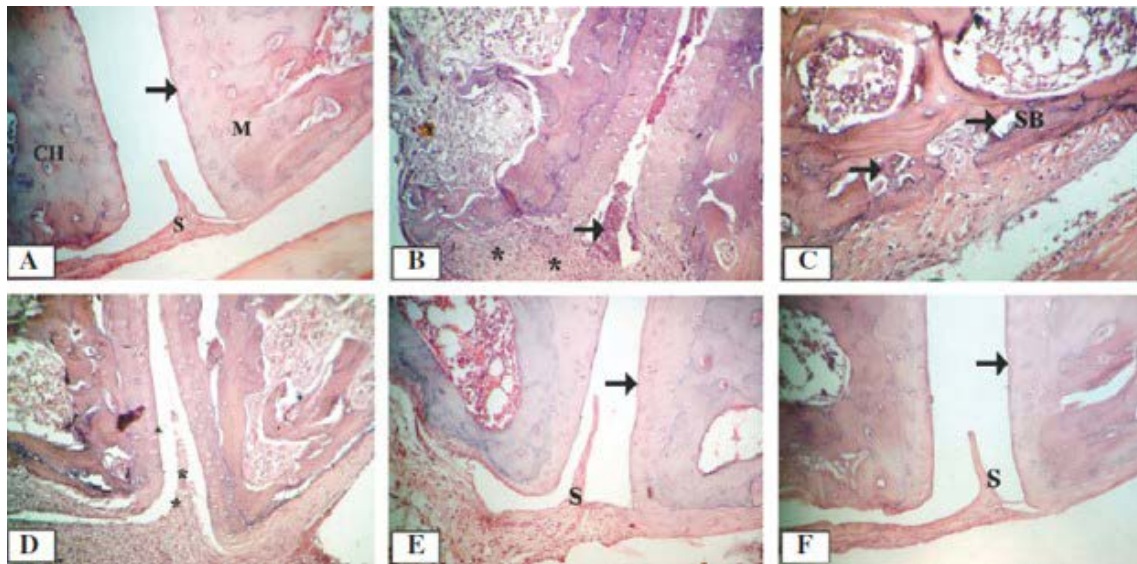


Figure 1. Histological Findings in the Knee Joint Model

Note. *S. lappa*: *Saussurea lappa*. **(A)** In control rats, the articular cartilage surface was well preserved (arrow), with a normal distribution of chondrocytes (CH), typical cell morphology, and an unbroken extracellular matrix (M). In addition, the synovial compartment surrounding the joint appeared normal (S). **(B)** Adjuvant monoarthritis rats showed prominent synovial enlargement and proliferation (arrow), along with conspicuous inflammatory cell invasion within the synovial tissue (asterisks). **(C)** These changes were associated with the deterioration of both cartilage and bone (arrows) and development of pannus tissue that penetrates the underlying subchondral bone (SB). **(D)** In AA rats treated with 200 mg/kg of *S. lappa*, there was a reduction in synovial inflammatory cell infiltration, and the synovial lining exhibited less hyperplasia (asterisks) compared with untreated AA animals. **(E)** In AA rats receiving 400 mg/kg *S. lappa*, the cartilage surface layer remained intact (arrow), and the synovial space around the joint was comparable to normal (S). **(F)** Similarly, AA rats treated with 600 mg/kg *S. lappa* maintained an intact surface layer (arrow) and a normal-appearing synovial space (S). Hematoxylin and eosin staining was used, and original magnifications were 200× for A, B, D, E, and F, and 400× for C.

Additionally, the allocation sequence was not accessible to participants, therapists, or outcome assessors prior to completion of the intervention and analysis.

Furthermore, a double-blind design was maintained such that participants, therapists, outcome assessors, and the statistical analyst remained unaware of group assignments. The active preparation and placebo were also packaged in identical containers differing only by a code label and were dispensed using unique codes (A001 to A094). In addition, the placebo was visually matched to the active oil by adding a small amount of yellow coloring to achieve the appearance of the pale-yellow active preparation while maintaining similar consistency. Moreover, study medications were provided to participants by a third person not involved in participant assessment or outcome measurement, further preserving blinding.

Interventions

In the intervention group, participants received topical *S. lappa* oil manufactured by EXIR Company (industrial identification No. 0467006866; Manufacturing License No. 127/19180; ISIC code 154315). In the control group, participants received a paraffin oil placebo prepared and packaged to match the active product. They applied a fingertip-sized amount (0.2–0.3 mL) of the assigned oil to the knee joint every 12 hours for 4 weeks.

Likewise, participants were instructed to avoid other analgesic medications during the study period, except for acetaminophen if pain became intolerable.

Outcomes

The primary outcomes were assessed using WOMAC

and VAS. Knee pain and functional outcomes were also evaluated using WOMAC (pain, physical function, and stiffness components), and knee pain intensity was assessed using VAS. Further, assessments were performed at baseline (before intervention initiation), at week 2, and at week 4 using standardized procedures and questionnaires administered at the same time intervals for all participants.

Timing of Outcome Assessments

VAS knee pain was recorded at baseline and at 15 days and 30 days after the initiation of treatment. Finally, WOMAC physical function and stiffness were recorded at baseline and at 15 days and 30 days after the initiation of treatment.

Statistical Analysis

Statistical analysis was planned according to a pre-specified analysis strategy consistent with Consolidated Standards of Reporting Trials recommendations. The analysis set(s) and primary endpoint definition, effect estimates, handling of missing data, and statistical tests were defined a priori in the statistical analysis plan, including specification of the primary comparisons between groups and the significance level (two-sided $\alpha = 0.05$). In addition, baseline characteristics were descriptively summarized by group. Efficacy analyses were also performed using the prespecified analysis set(s) (e.g., intention-to-treat and, if prespecified, per-protocol), with primary inference based on the intention-to-treat population. Further, the effect of the intervention on continuous outcomes (VAS and WOMAC components) was assessed using between-group statistical testing across follow-up time points, with the estimation of between-group differences

(and corresponding 95% confidence intervals) for the prespecified primary endpoint; the covariance structure and model terms for time and treatment were prespecified. Additionally, repeated measurements were analyzed using an appropriate repeated-measures framework (as defined in the analysis plan) and the main test corresponded to the prespecified treatment effect over time. Furthermore, assumptions required for the planned parametric models were checked using prespecified diagnostics; if assumptions were not met or if prespecified rules were triggered, the analysis was conducted using the alternative/robust approach stated in the analysis plan. Moreover, missing outcome data were addressed according to the prespecified strategy in the statistical analysis plan (e.g., maximum-likelihood estimation within the chosen model and/or sensitivity analyses such as multiple imputation, if planned). It should be noted that all results were reported according to the prespecified analysis plan, including adjusted *P*-values for any multiple comparisons, and all deviations from the plan were described in the manuscript.

Results

Initially, this study included 98 patients with KOA equally assigned to the treatment and control groups. During the study, there were 4 cases of shedding from both groups. Ultimately, 94 patients completed the study. Figure 2 displays the flow chart of the study process.

The WOMAC index is a tool for measuring the degree of improvement in patients with OA. The WOMAC consists of pain, stiffness, and physical function domains. Pain and stiffness are assessed using five and two sub-items, respectively, and physical function is measured with seventeen sub-items. Figure 3 illustrates WOMAC.

Each item is rated according to severity on the 0–4 scale, and a total WOMAC score is obtained by summing item scores (with the total range depending on the number of items used). Table 1 provides the total score before and

after treatment, reflecting the therapeutic effect of the intervention

Across all WOMAC subscales, *P*-values were less than 0.001, indicating highly statistically significant differences between the pre-treatment and post-treatment assessments. Furthermore, the 95% confidence intervals for all comparisons did not include zero, further confirming the statistical significance of the treatment effect. Therefore, the treatment could significantly reduce pain and stiffness while markedly improving physical function among patients with KOA.

Based on the results of group comparison, no noticeable change was observed in the placebo group for pain, stiffness, and physical activity. In the intervention group, pain, stiffness, and physical activity decreased from 14.10 to 8.63, from 5.63 to 3.87, and from 45.21 to 30.38, respectively.

In the assessment of the VAS score (range: 0–10), the mean score before treatment was 9.2, which decreased to 7.8 and 6.4 after 15 days and 30 days of treatment, respectively. This reduction was statistically significant, demonstrating a meaningful improvement in patient's pain levels following the intervention.

The placebo and intervention groups were compared before and after treatment using WOMAC scores (Table 2).

Figure 3 shows womac score sheet. No serious adverse events occurred during the trial, and none of the withdrawals were related to *S. lappa* treatment. Likewise, mild gastrointestinal complaints were reported in 7 participants in the *S. lappa* group and 4 participants in the placebo group. The incidence of these adverse events was not significantly different between groups ($P > 0.05$). Ultimately, the effectiveness of *S. lappa* in the treatment of KOA and the reduction of inflammation requires more extensive future research.

Discussion

OA is a chronic, degenerative joint disease involving the

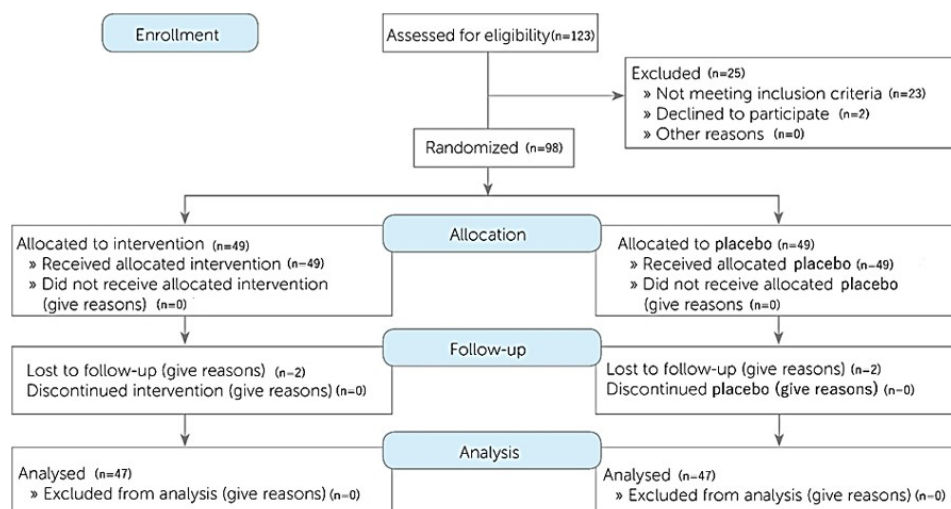


Figure 2. The CONSORT Flow Diagram for Screening, Enrollment, Allocation, Follow-up, and Analysis

Note. CONSORT: Consolidated Standards of Reporting Trials. During enrollment, participants were screened and those not meeting eligibility criteria, those who declined participation, and those excluded for other reasons were documented by arm. Following randomization, participants were followed for 4 weeks, and losses to follow-up were recorded with documented reasons. Analysis was conducted after the completion of the follow-up, with the number analyzed per group and reasons for exclusion from analysis reported for each arm in the CONSORT flow diagram

progressive loss of articular cartilage, inflammation of the synovial membrane, and subchondral bone changes. The condition is mediated by complex biochemical

Table 1. Comparison of WOMAC Subscale Scores Before and After Treatment (n = 94)

WOMAC Subscale	Before Treatment Mean ± SD	After Treatment Mean ± SD	Mean Difference (95% CI)	P-Value*
Pain	14.10 ± 4.10	8.63 ± 2.90	-5.47 (-6.50 to -4.44)	<0.001
Stiffness	5.63 ± 1.80	3.87 ± 0.50	-1.76 (-2.19 to -1.33)	<0.001
Physical function	45.21 ± 14.00	30.38 ± 10.30	-14.83 (-18.59 to -11.07)	<0.001

Note. Values are presented as means ± SD *P-value was obtained using paired t-test. SD: Standard deviation; 95% CI: 95% confidence interval; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index

processes, including increased oxidative stress, elevated inflammatory cytokines (e.g., IL-1 β and TNF- α), and the upregulation of cartilage-degrading enzymes (e.g., matrix metalloproteinases. *S. lappa*, also known as *Saussurea costus* or bitter Costus, is a medicinal plant traditionally used in Unani and Ayurvedic medicine. Recent pharmacological research supports its potential role in OA treatment due to its anti-inflammatory, antioxidant, and chondroprotective properties.

Studies have shown that *S. lappa* extracts can significantly reduce the expression of pro-inflammatory cytokines, including TNF- α and IL-1 β . This effect appears to be mediated through inhibition of the nuclear factor kappa B signaling pathway, which is a central regulator of inflammation in osteoarthritic joints¹⁶ The research

Table 2. Comparison of WOMAC Subscale Scores Between Treatment and Placebo Groups (n = 94)

WOMAC Subscale	Placebo Group (n = 94)			Treatment Group (n = 94)			Between-Group Comparison (Difference in Mean Change [95% CI])	P-Value*
	Before Treatment Mean ± SD	After Treatment Mean ± SD	Mean Change (95% CI)	Before Treatment Mean ± SD	After Treatment Mean ± SD	Mean Change (95% CI)		
Pain	14.10 ± 4.10	13.70 ± 4.20	-0.40 (-1.51 to 0.71)	14.10 ± 4.10	8.63 ± 2.90	-5.47 (-6.50 to -4.44)	-5.07 (-6.28 to -3.86)	<0.001
Stiffness	5.63 ± 1.80	5.26 ± 1.90	-0.37 (-0.88 to 0.14)	5.63 ± 1.80	3.87 ± 0.50	-1.76 (-2.19 to -1.33)	-1.39 (-1.90 to -0.88)	<0.001
Physical function	45.21 ± 14.00	45.21 ± 14.10	0.00 (-2.46 to 2.46)	45.21 ± 14.00	30.38 ± 10.30	-14.83 (-18.59 to -11.07)	-14.83 (-19.23 to -10.43)	<0.001

Note. WOMAC: The Western Ontario and McMaster Universities Osteoarthritis Index; SD: Standard deviation; CI: Confidence interval

The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)

Name: _____ Date: _____

Instructions: Please rate the activities in each category according to the following scale of difficulty:
0 = None, 1 = Slight, 2 = Moderate, 3 = Very, 4 = Extremely. Circle one number for each activity:

Pain	1. Walking	0	1	2	3	4
	2. Stair Climbing	0	1	2	3	4
	3. Nocturnal	0	1	2	3	4
	4. Rest	0	1	2	3	4
	5. Weight bearing	0	1	2	3	4
Stiffness	1. Morning stiffness	0	1	2	3	4
	2. Stiffness occurring later in the day	0	1	2	3	4
Physical Function	1. Descending stairs	0	1	2	3	4
	2. Ascending stairs	0	1	2	3	4
	3. Rising from sitting	0	1	2	3	4
	4. Standing	0	1	2	3	4
	5. Bending to floor	0	1	2	3	4
	6. Walking on flat surface	0	1	2	3	4
	7. Getting in / out of car	0	1	2	3	4
	8. Going shopping	0	1	2	3	4
	9. Putting on socks	0	1	2	3	4
	10. Lying in bed	0	1	2	3	4
	11. Taking off socks	0	1	2	3	4
	12. Rising from bed	0	1	2	3	4
	13. Getting in/out of bath	0	1	2	3	4
	14. Sitting	0	1	2	3	4
	15. Getting on/off toilet	0	1	2	3	4
	16. Heavy domestic duties	0	1	2	3	4
	17. Light domestic duties	0	1	2	3	4

Total Score: _____ / 96 = _____ %

Comments / Interpretation (to be completed by therapist only):

Figure 3. WOMAC Score Sheet Showing Questionnaire Structure and Scoring Categories for Pain, Stiffness, and Physical Function

Note. WOMAC: The Western Ontario and McMaster Universities Osteoarthritis Index

evaluated the TNF- α inhibitory potential of sesquiterpenes obtained from *S. lappa* root extracts. The hexane and ethyl acetate fractions demonstrated pronounced activity, with the half-maximal inhibitory concentration values of 0.5 $\mu\text{g/mL}$ and 1.0 $\mu\text{g/mL}$, respectively. Guided by these results, the extracts were fractionated chromatographically, resulting in the isolation of ten sesquiterpenes^{1,10,44} One investigation also assessed the in vitro anti-inflammatory effects of cynaropicrin a sesquiterpene lactone from *S. lappa* by examining its impact on TNF- α and nitric oxide production as well as lymphocyte proliferation. Cynaropicrin markedly suppressed TNF- α release in lipopolysaccharide-stimulated murine RAW264.7 macrophages and in differentiated human U937 macrophages, leading to a pronounced reduction in TNF- α levels.⁴⁵

Oxidative stress plays a key role in the degeneration of cartilage. Extracts of *S. lappa* have shown strong free radical scavenging activity, thereby reducing oxidative damage and slowing the progression of joint destruction.⁴⁶ One study evaluated the potential of *S. lappa* C.B. Clarke as a source of antioxidant agents. Root samples were fractionated using different solvents and their antioxidant activities underwent evaluation. Total phenolic and flavonoid contents were quantified using the Folin–Ciocalteu colorimetric assay and the aluminum nitrate method, respectively.⁴⁷

Costus root of the Asteraceae family is used in Ayurveda for chronic rheumatism. Its constituents (i.e., cynaropicrin and dehydrocostus) inhibit TNF- α production and suppress lipopolysaccharide-induced nitric oxide in cell studies. Thus, *S. lappa* may have anti-arthritis and anti-inflammatory potential, but clinical trials are needed to confirm this issue.⁴⁸ MMP-13 is a critical enzyme involved in cartilage matrix breakdown. In preclinical studies, *S. lappa* extract reduced MMP expression, thereby suggesting a potential chondroprotective effect, which may help in preserving cartilage integrity in OA patients.^{49,50}

In addition to its anti-inflammatory role, *S. lappa* has shown analgesic (pain-relieving) activity in animal models, potentially offering symptomatic relief from joint pain and improving mobility in OA patients.⁵¹ A comprehensive review of *S. lappa* revealed a wide range of bioactive components (e.g., sesquiterpene lactones, flavonoids, and phenolics) that contribute to its pharmacological profile.⁵²

A large body of research indicates that oxidative stress contributes importantly to the development of RA. According to evidence from RA patient sera and synovial fluid, oxidative processes intensify manifested by elevated activity of pro-oxidant enzymes alongside reduced antioxidant availability. Analyses of synovial fluid and affected tissues in RA further demonstrate molecular and biochemical injury, including oxidative impairment of hyaluronic acid, accumulation of lipid peroxidation products, oxidation of low-density lipoproteins, and increased protein carbonyls resulting from protein oxidation. Based on these findings, it is reasonable to propose that the antioxidant capacity of the *S. lappa* extract may lower overall oxidative burden (total oxidative capacity) while boosting the body's antioxidant defenses

(total antioxidant capacity) as inflammation progresses, supporting the rationale for using this plant extract as a therapeutic option in RA.⁴⁸

Conclusions

In general, the findings of this study investigating the effects of *S. lappa* on pain and functional outcomes in patients demonstrated some positive trends, particularly in pain reduction and functional mobility. The *S. lappa* group showed significant improvements in various measures, including the VAS, WOMAC scores. However, the lack of consistent statistically significant differences between the *S. lappa* and placebo groups across most outcomes suggests that the overall efficacy of the intervention may not be robust. While the reduction in analgesic consumption in the *S. lappa* group indicates a potential benefit in pain management, the findings highlight the need for further research. Accordingly, future studies with larger sample sizes, longer follow-up periods, and more rigorous methodologies are necessary to better understand the therapeutic potential of *S. lappa*. Additionally, the absence of reported adverse events during the trial suggests that *S. lappa* is safe and well-tolerated, making it a candidate for further exploration in the management of pain and functional impairment in patients with OA or similar conditions. Overall, while the initial results are promising, more comprehensive studies are required to establish definitive conclusions regarding the efficacy of *S. lappa* as a treatment option.

Acknowledgments

This study was conducted as part of the first author's Ph. D. dissertation submitted to Tabriz University of Medical Sciences ethics approval : IR.TBZMED.REC.1402.317.

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Funding

This study was financially supported by the Research Center of Tabriz University of Medical Sciences, Tabriz, Iran.

Data availability statement

The data supporting the findings of this study are available upon request from the corresponding author.

Ethical approval

Ethical approval for this study was obtained from the Ethics Committee of Tabriz University of Medical Sciences (approval No. 1402. 317).

Consent for publication

Not Applicable.

Conflict of interests

The authors declare that they have no competing interests.

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