

⇒ Research Article



Topical Piroxicam Gel versus Satureja khuzestanica Jamzad 3% Ointment for Pain Relief in Patients with Osteoarthritis of the Knee; A Randomized Controlled Trial

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Abstract

Background: Osteoarthritis (OA) is a common disease without definite and exact treatment. Interventions such as chemical drugs, physiotherapy, and even surgery are suggested for treatment. Herbal medicine, which is currently very popular, has also been suggested for treatment because of fewer side effects, low cost, and the possibility to use it topically home. Satureja khuzestanica jamzad, the native plant of Lorestan and Khuzestan, is known for its analgesic effects.

Objective: We aimed to compare the effect of Satureja khuzestanica jamzad 3% ointment with piroxicam gel for pain relief in patients with knee osteoarthritis.

Methods: 70 patients with mild to moderate knee OA were randomly divided into experimental groups (essential oil extract of Satureja khuzestanica jamzad 3% or piroxicam gel). The severity of pain was recorded at baseline, and after one and two weeks by visual analogue scale. ANOVA was used for data analysis and the effect size was computed by Cohen's d.

Results: Reduction of pain was seen in both groups and group comparisons also showed a significant difference ($P < 0.05$). The more effect size was detected in the group receiving Satureja khuzestanica jamzad 3% ointment compared with the piroxicam group.

Conclusion: The topical use of Satureja khuzestanica jamzad 3% essential oil is a good choice to reduce pain in patients with knee OA. It may be used as a drug in phonophoresis.

Keywords: Essential oil, Extract, Osteoarthritis, Satureja khuzestanica jamzad, Piroxicam

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Background

Osteoarthritis (OA) is a slowly progressive non-inflammatory degenerative joint disease which affects all joints, especially the hip and knee joints. At the beginning of disease, the joint cartilage is damaged leading to biochemical changes. The first and most common sign and symptoms are inflammation and pain (1-3). Different treatments include drug taking, drug injection, physiotherapy, topical and dermal use of chemical and herbal ointment. Intra-articular injection of hyaluronic acid or glucocorticoids is another choice for treatment. Oral medications have several side effects such as stomach complications, or forgetting to take them (4, 5).

Phonophoresis can transfer topical drugs such as piroxicam gel or other herbal and chemical drugs from

the skin surface to subcutaneous tissues by ultrasound (6, 7). Herbal medicine has recently become common for pain relief and inflammation in different musculoskeletal disorders. Satureja khuzestanica Jamzad is one of the native plants of the southern regions of Iran. Khuzestani safflower is a plant with a height of about 30 cm, with sub-branches, dense leaves and covered with white, thin and cup-shaped trichomes with a wide and circular base (8, 9). The analgesic, antiseptic, appetizing, anti-inflammatory, and anti-diabetic properties of this plant have been approved. 10% Dentol drops are currently available and used to treat toothache.

Anti-inflammatory and analgesic properties of carvacrol have been confirmed to be the main substances of Khuzestani safflower essential oil (10-12). The

essential oil of the plant contains phenolic compounds such as carvacrol (13) and flavonoids (14). Amanlou and colleagues examined the anti-inflammatory effects of Khuzestani safflower hydroalcoholic extract on rats' toes compared to morphine and indomethacin (15). The analgesic and anti-inflammatory effects have been studied in patients with dysmenorrhea and neuralgia (16, 17). Inhibition of prostaglandin synthesis and of COX-2 enzyme is main mechanism of carvacrol for reduction of joint inflammation. Prostaglandins are one of the most important mediators of inflammation, and inhibition of their production by nonsteroidal anti-inflammatory drugs such as ibuprofen reduces inflammation (14, 18). On the other hand, the positive effect of piroxicam phonophoresis compared with conventional ultrasound therapy has been shown in mild to moderate symptomatic knee OA (19). Luksurapan and co-workers also observed the superiority of piroxicam phonophoresis compared with ultrasound in reducing pain and improving knee function (19, 20).

Piroxicam, as a nonsteroidal anti-inflammatory drug (NSAID), is used in musculoskeletal and joint disorders. Piroxicam is more formulated in pharmaceutical industries because of its oil-free and water-removable (do you mean soluble?) property, efficacy, and harmless dermal effects (20). The most adverse effects of piroxicam are reported in the gastrointestinal track, and bleeding may occur with piroxicam suppositories (5).

Considering the analgesic and anti-inflammatory properties of safflower plant of *Satureja khuzestanica* and the high prevalence of OA, as well as the positive effect of piroxicam phonophoresis, we aimed to compare the effect of *Satureja khuzestanica* with piroxicam for pain reduction in patients with knee OA.

Patients and Methods

This study was a randomized, double-blind, controlled trial registered in the Iranian Registry of Clinical Trials (IRCT138902043760N2).

Plant material and preparation of extract and essential oil

Satureja khuzestanica plants were collected from Khorramabad city and transferred to the laboratory. Separation and measurement were done with gas chromatography machine (Shimadzu 17 A [GC/MS], Country?) coupled with mass spectrometry (model QP5050A, Company? Country?). The British pharmacy clevenger apparatus was used to make essential oils. The essential oil of *Satureja khuzestanica* jamzad 3% was prepared by hydro distillation with a clevenger device in the laboratory.

Participants

85 patients were referred to the clinic by a specialist

physician. Patients with mild to moderate OA were included. Pregnant patients, lactating women, history of knee surgery, corticosteroid injections, taking oral or topical analgesics, or those allergic to the ointment compounds were excluded (20).

Patients with mild OA had greater bone spur in radiographs, healthy size cartilage with normal space between the bones without rubbing or scraping one another and sufficient synovial fluid. Sometimes the patients experienced pain after a long day of walking or running or stiffness in the joint when it was not used for several hours, or tenderness when kneeling or bending. Patients with moderate OA had cartilage damage, narrowing gap between the bones with cartilage loss, pain and discomfort during daily activities, such as running, walking, kneeling, and bending. Early signs of joint inflammation and synovitis are also common.

74 patients were randomly assigned to piroxicam or *Satureja Khosetanica* herbal groups by picking up envelopes with numbers 1 or 2 written on them. The more painful side was treated regardless of the dominant or non-dominant side. 35 participants in each group (10 men and 25 women in the *Satureja Khosetanica* group and 8 men and 27 women in the piroxicam group) received the assigned treatment. (35+35=70, not 74. What happened to the other 4?) All patients gave their written informed consent to participate. At the beginning of treatment, we asked from patients not to use other analgesic treatments such as acetaminophen or other topical ointments during two weeks.

The first group (n=35) received Khuzestani safflower essential oil ointment 3% and the second group (n=35) as a control group received 5% piroxicam oil. Essential oil extract of Khuzestani safflower 3% was prepared and given to patients for topical use for 2 weeks, 10 minutes twice a day on the painful sites of the knee joint. The other group received 5% piroxicam ointment for 2 weeks, 10 minutes twice a day on the painful sites of the knee joint (Figure 1). Pain reduction was assessed at baseline, one week, and 2 weeks after treatment by Visual Analogue Scale (VAS). Individual characteristics such as height, weight, body mass index (BMI) and age were recorded before treatment. We did not perform data normalization based on weight or leg length.

Results

The baseline characteristics of the patients is shown in Table 1. The mean pain intensity is reported in Table 2 at baseline, one week, and 2 weeks after use the essential oil of *Satureja khuzestanica* jamzad or piroxicam gel. Both treatments had a significant effect on reduce patients' pain ($P < 0.05$). (It was better to write the exact P values)

There was no significant difference in pain severity between the two groups at baseline. Significant differences were seen between the *Satureja khuzestanica* jamzad

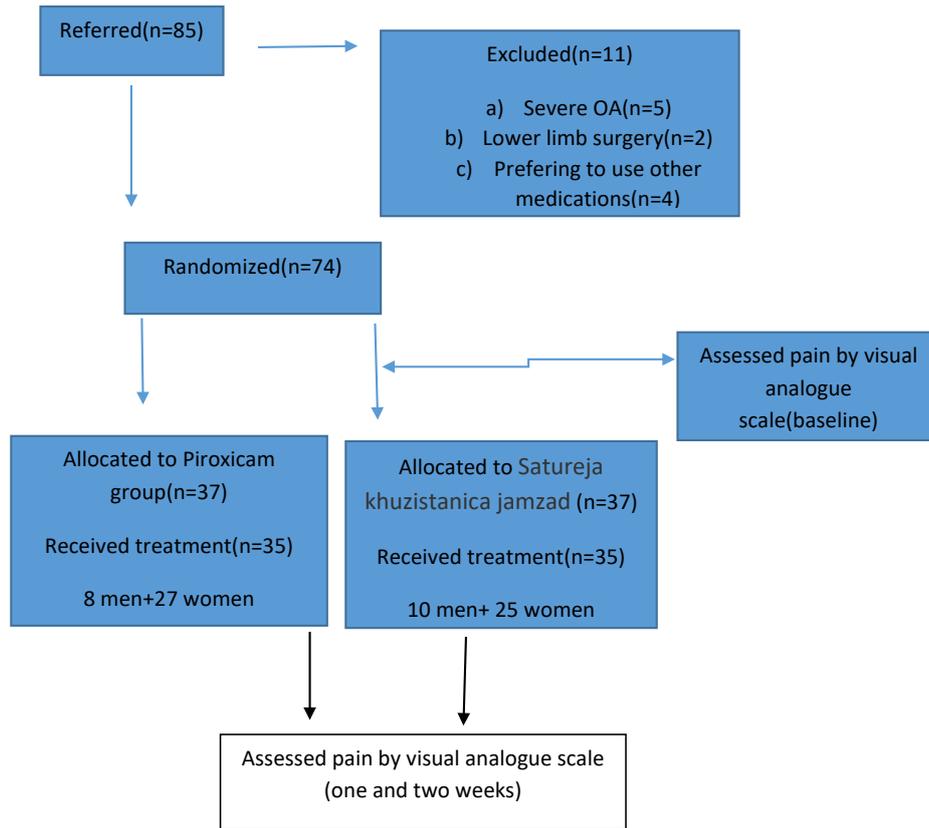


Figure 1. CONSORT flow diagram for randomized, controlled trials

Table 1. Demographic data of subjects (Mean ± SD)

Group	Height	Age	Weight	BMI
1	158.6 ±19.6	53.5±12.3	15.1±65	8.06 ± 26.4
2	167.8±19.6	55.2±17	13±70.8	4.5±25.07

essential oil group (group 1) and the piroxicam 5% group ($P < 0.001$) after one and two weeks. The highest effect size was seen in Satureja khuzestanica jamzad essential oil after one week (1.94). The comparison between two groups also showed a high effect size after one and two weeks in favor of the Satureja khuzestanica jamzad group. Cohen's d effect size in the range of 0.2 or less indicates a low effect, 0.6 and 0.8 indicates a medium effect, and above that is considered as a high effect (21).

Discussion

Despite pharmacological and non-pharmacological treatments for OA, there is no definite intervention for

patients with knee OA. Moreover, oral medications have several side effects. To reduce these side effects topical use of drugs such as topical NSAIDs is recommended (4, 5). Currently, the use of herbal medicine has received special attention and seems to have fewer adverse effects. In previous studies the analgesic and anti-inflammatory effects of Satureja khuzestanica jamzad have been proven (14, 18, 22-24).

According to our study, the effect of a solution containing Satureja khuzestanica jamzad 3% essential oil on pain reduction was greater than piroxicam gel 5% in patients with mild to moderate OA. These findings suggest that Satureja khuzestanica jamzad might be an appropriate option in the elderly or those at risk of adverse events from oral NSAIDs.

The main mechanism of pain relief of Satureja khuzestanica jamzad is unknown. Pain reduction effects in previous studies are attributed to central and

Table 2. VAS variables before and after treatment (Mean ± SD)

Group	Baseline	1 week	Effect Size	P value	2 weeks	Effect Size	P value
Satoria Khostanica 3%	67.94±16.1	31.18±21.43	1.94	<0.05	11.62±19	0.97	<0.05
Piroxicam5%	68.04±14.03	57.14±15.66	0.73	<0.05	46.25±20.17	0.6	<0.05
Analysis between 2 groups			1.38	<0.001		1.76	<0.001

environmental mechanisms. The main component of this plant is carvacrol and flavonoids, and the analgesic effects are also related to carvacrol compounds (13, 14, 18). In the present study, the percentage of carvacrol was estimated to be 77.51%.

Prostaglandin synthesis is inhibited by carvacrol leading to anti-inflammatory effects. (14, 18). Also, the anti-inflammatory effect of carvacrol has been attributed to COX-2 enzyme inhibition (17). Because of the increasing analgesic effect of low doses of morphine by *Satureja khuzestanica* jamzad, it seems that this plant can be used alone or in combination with other analgesic drugs (25). Some advantages of this herbal ointment are rapid effect on pain relief, topical use, and suitable acceptance by patients.

Our results revealed the superiority of *Satureja khuzestanica* jamzad 3% ointment compared with piroxicam 5% in pain reduction. Therefore, because of the frequent use of phonophoresis in physiotherapy, it is suggested to use *Satureja khuzestanica* jamzad by phonophoresis as a modality for pain relief in physiotherapy. Phonophoresis of piroxicam was more effective than US (should be spelled out) alone on reduction of pain and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain scores (19, 20).

Our results revealed superiority of herbal ointment to piroxicam in reduction of pain in patients with mild to moderate OA. There are some limitations in our study. For example, we did not check normality of data based on the patient's weight or length of lower limb. Another limitation was that we offered to control their activities during treatment but we could not control at home. We selected the painful side and we did not compare the dominant or non-dominant side or women and men.

Conclusion

Application of *Satureja khuzestanica* jamzad 3% and piroxicam 5% can relief pain in patients with knee OA, but the effect size of pain relief in was greater the herbal group. Further studies are needed to clarify what percent of *Satureja khuzestanica* jamzad ointment is more effect in reducing pain.

Authors' Contribution

All authors contributed to the design and implementation of the research, and Dr. Otadi contributed to the analysis of the results and to the writing of the manuscript

Conflict of Interests

None.

Ethical Approval

Ethical code is 159 that confirmed in Lorestan University of Medical Sciences.

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References

1. Deshpande MM, Patil CB. Heel pain and phonophoresis. *J Indian Med Assoc.* 2010;108(6):365.
2. Yildiz N, Atalay NS, Gungen GO, Sanal E, Akkaya N, Topuz O. Comparison of ultrasound and ketoprofen phonophoresis in the treatment of carpal tunnel syndrome. *J Back Musculoskelet Rehabil.* 2011;24(1):39-47. doi: 10.3233/bmr-2011-0273.
3. Zhang W, Moskowitz RW, Nuki G, Abramson S, Altman RD, Arden N, et al. OARSI recommendations for the management of hip and knee osteoarthritis, part II: OARSI evidence-based, expert consensus guidelines. *Osteoarthritis Cartilage.* 2008;16(2):137-62. doi: 10.1016/j.joca.2007.12.013.
4. Zhang W, Doherty M. EULAR recommendations for knee and hip osteoarthritis: a critique of the methodology. *Br J Sports Med.* 2006;40(8):664-9. doi: 10.1136/bjism.2004.016840.
5. Rutjes AW, Nuesch E, Sterchi R, Juni P. Therapeutic ultrasound for osteoarthritis of the knee or hip. *Cochrane Database Syst Rev.* 2010(1):CD003132. doi: 10.1002/14651858.CD003132.pub2.
6. Tascioglu F, Kuzgun S, Armagan O, Ogutler G. Short-term effectiveness of ultrasound therapy in knee osteoarthritis. *J Int Med Res.* 2010;38(4):1233-42. doi: 10.1177/147323001003800404.
7. Farsam H, Amanlou M, Radpour MR, Salehinia AN, Shafiee A. Composition of the essential oils of wild and cultivated *Satureja khuzistanica* Jamzad from Iran. *Flavour Fragr J.* 2004;19(4):308-10. doi: 10.1002/ffj.1300.
8. Matloubi Moghaddam F, Moridi Farimani M, Salahvarzi S, Amin G. Chemical constituents of dichloromethane extract of cultivated *Satureja khuzistanica*. *Evid Based Complement Alternat Med.* 2007;4(1):95-8. doi: 10.1093/ecam/nel065.
9. Seghatoleslami S, Samadi N, Salehnia A, Azimi S. Antibacterial activity of endemic *Satureja Khuzistanica* Jamzad essential oil against oral pathogens. *Iran Endod J.* 2009;4(1):5-9.
10. Arshadi Bostanabad M, Hiradfar A, Mohammadpoorasl A, Javadzadeh Y, Khalvati B, Alvandnezhad T. The effect of mucoadhesive gel containing *Satureja hortensis* extract 1% on severity of chemotherapy-induced mucositis pain in children: a randomized clinical trial. *Int J Pediatr.* 2018;6(5):7605-14. doi: 10.22038/ijp.2017.25259.2143.
11. Hosain Zadegan H, Delfan B. Evaluation of antibiofilm activity of dentol. *Acta Med Iran.* 2009;47(1):35-40.
12. Fazel M, Omidbeygi M, Barzegar M, Naghdi Badi H. Influence of heating on antiradical activity of essential oils of thyme, summer savory and clove by 2, 2-diphenyl-1-picrylhydrazyl (DPPH•) method. *J Med Plants.* 2007;6(22):54-63. [Persian].
13. Abdollahi M, Salehnia A, Mortazavi SH, Ebrahimi M, Shafiee A, Fouladian F, et al. Antioxidant, antidiabetic, antihyperlipidemic, reproduction stimulatory properties and safety of essential oil of *Satureja khuzestanica* in rat in vivo: a oxico-pharmacological study. *Med Sci Monit.*

- 2003;9(9):BR331-5.
14. Amanlou M, Fazeli MR, Arvin A, Amin HG, Farsam H. Antimicrobial activity of crude methanolic extract of *Satureja khuzistanica*. *Fitoterapia*. 2004;75(7):768-70. doi: 10.1016/j.fitote.2004.09.005.
 15. Amanlou M, Babaee N, Saheb-Jamee M, Salehnia A, Farsam H, Tohidast Akrad Z. Efficacy of *Satureja khuzistanica* extract and its essential oil preparations in the management of recurrent aphthous stomatitis. *DARU J Pharm Sci*. 2007;15(4):231-5. [Persian].
 16. Delfan B, Hashemnia M, Javanbakht A, Nazari M, Jebreily R, Birjandi M, et al. The effect of *Satureja khuzestanica* essential oil on the pain of patients with PHN. *Yafteh*. 2010;11(5):25-34. [Persian].
 17. Landa P, Kokoska L, Pribylova M, Vanek T, Marsik P. In vitro anti-inflammatory activity of carvacrol: inhibitory effect on COX-2 catalyzed prostaglandin E(2) biosynthesis. *Arch Pharm Res*. 2009;32(1):75-8. doi: 10.1007/s12272-009-1120-6.
 18. Monisha R, Manikumar M, Krishnakumar A. Evaluating the effectiveness of phonophoresis by piroxicam and dimethyl sulfoxide for women's with osteoarthritis knee joint. *Asian J Pharm Clin Res*. 2018;11(6):329-31. doi: 10.22159/ajpcr.2018.v11i6.24615.
 19. Luksurapan W, Boonhong J. Effects of phonophoresis of piroxicam and ultrasound on symptomatic knee osteoarthritis. *Arch Phys Med Rehabil*. 2013;94(2):250-5. doi: 10.1016/j.apmr.2012.09.025.
 20. Soni A, Kiran A, Hart DJ, Leyland KM, Goulston L, Cooper C, et al. Prevalence of reported knee pain over twelve years in a community-based cohort. *Arthritis Rheum*. 2012;64(4):1145-52. doi: 10.1002/art.33434.
 21. Cohen J. *Statistical Power Analysis for the Behavioral Sciences*. 2nd ed. Hillsdale, NJ: Lawrence Earlbaum Associates; 1988.
 22. Menichini F, Conforti F, Rigano D, Formisano C, Piozzi F, Senatore F. Phytochemical composition, anti-inflammatory and antitumour activities of four *Teucrium* essential oils from Greece. *Food Chem*. 2009;115(2):679-86. doi: 10.1016/j.foodchem.2008.12.067.
 23. Botelho MA, Rao VS, Montenegro D, Bandeira MA, Fonseca SG, Nogueira NA, et al. Effects of a herbal gel containing carvacrol and chalcones on alveolar bone resorption in rats on experimental periodontitis. *Phytother Res*. 2008;22(4):442-9. doi: 10.1002/ptr.2325.
 24. Saberi A, Sepehrib G, Esmaeili-Mahani S, Rasoulia B, Sheibani V, Esmaeilpour K, et al. *Satureja khuzestanica* extract elicits antinociceptive activity in several model of pain in rats. *J Appl Sci*. 2013;13(5):729-35. doi: 10.3923/jas.2013.729.735.
 25. Hajhashemi V, Zolfaghari B, Yousefi A. Antinociceptive and anti-inflammatory activities of *Satureja hortensis* seed essential oil, hydroalcoholic and polyphenolic extracts in animal models. *Med Princ Pract*. 2012;21(2):178-82. doi: 10.1159/000333555.