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.

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

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
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 phophoresis 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 phophoresis 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 phophoresis, 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 Khorrarambad 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 Saturia 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 Satura 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 acetaminopen or other topical ointments during two weeks.

The first group (n = 35) received Khuzestani saffower 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

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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 peripheral analgesic effects. These mechanisms include enhancement of gamma-aminobutyric acid (GABA) neurotransmission, inhibition of the release of substance P (a pain mediator), and reduction of prostaglandin production in the peripheral nervous system (14, 18).

**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  |

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

| Group             | Baseline  | 1 week     | Effect Size | \(P\) value | 2 weeks  | Effect Size | \(P\) value |
|-------------------|-----------|------------|-------------|-------------|----------|-------------|-------------|
| Satureja Khuzistanica 3% | 67.94±16.1 | 31.18±21.43| 1.94        | <0.05       | 11.62±19 | 0.97        | <0.05       |
| Piroxicam 5%      | 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      |            | 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 relieve 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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