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Original Article

The Effect of St. John's Wort Oil (*Hypericum Perforatum L.*) in Knee Osteoarthritis: A Randomized Controlled and Qualitative Study

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ABSTRACT

Background: Reducing pain and improving physical function are critical in the treatment of osteoarthritis. Although individuals use St. John's Wort oil to relieve pain due to osteoarthritis, no scientific research has been found investigating its effectiveness.
Aim: This study investigated the effect of St. John's Wort oil on pain intensity and physical functions in people with knee osteoarthritis.
Methods: This study adopted a single-blind, randomized, placebo-controlled, and qualitative mixed design. The sample consisted of 60 patients randomized into intervention (n = 30) and placebo control (n=30) groups. The experimental group participants were treated with topically St. John's Wort oil three times a week for 3 weeks, and the placebo control group participants were treated with olive oil three times a week for 3 weeks. Quantitative data were collected using a patient identification form, the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), and the Visual Analogue Scale. Qualitative data were collected through semi-structured interviews.
Results: The experimental group had a significantly lower mean Visual Analog Scale score in the first, third, and fourth follow-ups than the control group. The experimental group had significantly lower mean WOMAC-pain, WOMAC-stiffness, and WOMAC-physical function subscale scores in the last follow-up than in the first follow-up. The qualitative data agreed with the quantitative data.
Conclusions: The results show that St. John's Wort oil helps people with knee osteoarthritis feel less pain and become physically more active. Additional research is warranted to better understand the effect of St. John's Wort oil on pain intensity and physical functions in people with knee osteoarthritis.
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Osteoarthritis is characterized by progressive deterioration of articular cartilage, and functional impairment (Huang et al., 2018). Osteoarthritis is one of the most important causes of pain and disability in older adults as it results in swelling and stiffness in the joints (Magni et al., 2021). When the lifetime risk of symptomatic knee OA is evaluated with different groups and methods, it has been reported that it varies between 15% and 45% (Allen et al., 2022). In 2020, there were around 654.1 million individuals (40 years and older) with knee osteoarthritis worldwide (Cui et al., 2020). Osteoarthritis is an important public health problem because it causes pain and disability. Pain and impaired functionality due to osteoarthritis negatively affect activities of daily living and impair quality of life (Al-Omari & Hill, 2020; Evaniew & Evaniew, 2017).

In folk medicine, St. John's Wort is a painkiller and antirheumatic (Aynaoğlu Hakverdi & Önder, 2022; Jarić et al., 2007). People use the oil-soluble extract of St. John's Wort to treat and heal muscle pain, varicose veins, burns, and rheumatic diseases (Kalaba et al., 2015). St. John's Wort contains quercetin, hyperoxide, quercitrin, rutin, hypericin, kaempferol, hyperforin, and biapigenin, which have neuroprotective activity due to their antioxidant properties (Oliveira et al., 2016). Research also shows that St. John's Wort treats trigeminal neuralgia (Assiri et al., 2017). Animal studies suggest that St. John's Wort helps relieve neuropathic pain (Bukhari et al., 2004; Galeotti et al., 2010, 2014; Galeotti & Ghelardini, 2013; Stojanović et al., 2016). Seferos et al. (2016) documented that St. John's Wort restored bone mass in rats (Seferos et al., 2016). For example, Galeotti and Ghelardini (2013) found that hypericin (one of the principal active constituents of St John's wort) helped relieve migraine pain in mice (Galeotti & Ghelardini, 2013), while Galeotti et al. (2014) determined that St. John's Wort seeds together with an extract of feverfew (Chrysanthemum Parthenium) were effective in relieving mechanical hyperalgesia in

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mice (Galeotti et al., 2014). Uchida et al. (2008) also documented that St. John's wort, devil's claw (Harpagophytum Procumbens), and grape seed extracts had antinociceptive effects (Uchida et al., 2008). Nowacki et al. (2015) found that a hydroalcoholic extract from St. John's Wort, Valeriana officinalis, and Piper methysticum effectively reduced orofacial pain in mice without damaging the liver (Nowacki et al., 2015). Galeotti et al. (2014) conducted a study on both mice and healthy volunteers. They found that St. John's Wort enhanced the analgesic effect of morphine (Galeottti et al., 2014). St. John's Wort interacts with some medicines. Although rare, it also causes dizziness, dry mouth, and allergic dermal reactions. Some studies suggest that St. John's Wort may lead to reduced efficacy of some medicines (Aşçı et al., 2007; Johne et al., 1999). St. John's wort oil has no significant side effects when applied to the skin. However, if exposed to sunlight, it increases the skin's sensitivity to the sun. Therefore, it is recommended to avoid exposure to sunlight after application (Wölfle et al., 2014). Although people use St. John's Wort to relieve osteoarthritis-related pain, there is no scientific research investigating its effectiveness. Therefore, this study investigated the effect of St. John's Wort oil on pain intensity and physical functions in people with knee osteoarthritis.

Methods

Aim

This study investigated the effect of St. John's Wort oil on pain intensity and physical functions in people with knee osteoarthritis.

Study Design

This study adopted a randomized, placebo-controlled, and qualitative mixed design. Figure 1 shows the Consolidated Standards of Reporting Trials (CONSORT) flow diagram of the quantitative stage. Qualitative data were collected using a semi-structured interview questionnaire.

Participants

The study was conducted in the physical therapy and rehabilitation outpatient clinic of a public hospital in Türkiye. The study population consisted of all patients admitted to the outpatient clinic for osteoarthritis-related pain. Data were collected between December 2017 and August 2018. A pilot study was conducted with five patients before data collection.

Patients were recruited based on certain inclusion criteria: (1) being older than 35 years of age; (2) being literate (able to write and read; people who do not have any graduation but can read and write); (3) planning no pregnancy during the study; (4) not being pregnant; (5) having been diagnosed with knee osteoarthritis according to ACR (American College of Rheumatology) criteria; (6) having had knee pain for the past month; (7) needing analgesics for more than 15 days in a month; (8) having osteoarthritis-related knee pain despite routine treatment with analgesics; (9) having a Visual Analog Scale (VAS) score of $\geq$4 on one knee; (10) speaking Turkish; (11) having no communication problems; and (12) volunteering (Barthel et al., 2009; Kooshki et al., 2016). The exclusion criteria in the study are as follows: (1) Pregnant; (2) having a physical disability in the area where the application will be made; (3) having any skin disease in the area to be treated; (4) having large scar tissue in the area to be treated; (5) having a history of physical trauma in the last three months in the area to be treated; (6) having any peripheral vascular disease in the area to be treated; (7) having inflammatory joint disease; (8) having a history of rheumatoid arthritis and fibromyalgia; (9) using any complementary and integrative (integrated) health application in the past 3 months; (10) those who have undergone intra-articular treatment in the past 3 months; (11) receiving pain blocking treatment in the past year; (12) receiving physical therapy in the last three months and during the application; and (13) patients with 2 or more pain in the other knee according to the VAS scale were not included in the study (Barthel et al., 2009; Kooshki et al., 2016).

Randomization and Blinding

Patients diagnosed with osteoarthritis by a physical therapy and rehabilitation specialist according to ACR criteria were randomized into the study by the University Biostatistics Unit. The initial sample consisted of 72 patients divided into intervention (n =36; St. John's wort oil) and placebo control (n = 36; olive oil) groups. However, six experimental group participants were excluded because they either could not be contacted on the phone during the follow-ups (n =4) or stated that they would be out of town for a long time (n =2). Six control group participants were also excluded because they either could not be contacted on the phone during the follow-ups (n =3), did not want to keep up with the intervention (n=1), or wanted to withdraw from the study (n=2). Therefore, the final sample consisted of 30 experimental and 30 control group participants (Fig. 1). Participants were called by the researcher once a day and reminded to apply the oil and put a mark on the form. At the same time, a home visit was made at the end of each week and a face-to-face interview was held. Therefore, participants had no missing data.

This study was a single-blind experimental clinical trial. All participants were briefed on the group assignment based on the recommendations of the Clinical Research Ethics Committee. Participants neither had side effects nor gave negative feedback about the interventions.

Interventions

The researcher briefed all patients about the research purpose and procedure. She obtained informed consent from those who agreed to participate. He then administered the data collection forms. He showed each participant how to use the oil. Participants were given the application procedure (Fig. 2). These applications took about 20 minutes. Face-to-face interviews were conducted with participants for 3 weeks to fill in the data collection forms as described in the procedure. The researcher conducted semi-structured interviews with participants at the beginning and end of the interventions. Then, she conducted a face-to-face interview with each participant and administered the patient identification form, VAS, and WOMAC.

The experimental and control groups underwent the same procedure, except for the type of oil. St. John's Wort oil is obtained by keeping the flowering parts of the plant in olive oil under the sun for 15 days. St. John's wort oil and olive oil used in the study were purchased from Helvacizade Gida Ilac ve Kimya. The experimental group participants were treated with St. John's Wort oil topically, while the control group participants were treated with olive oil. Each participant was given 50 mL of oil in dark bottles.

The researcher showed each participant how to apply oil to their knee. She explained the Oil Application Protocol (Fig. 2) and told them to apply the oils on their knees. The participants applied the oils alone or had their family members apply them. A form was created for the participants to regularly record their practices. They recorded how they applied the oils, what time they took painkillers, how many painkillers they took, and whether there were any side effects. Analgesic doses used by the participants

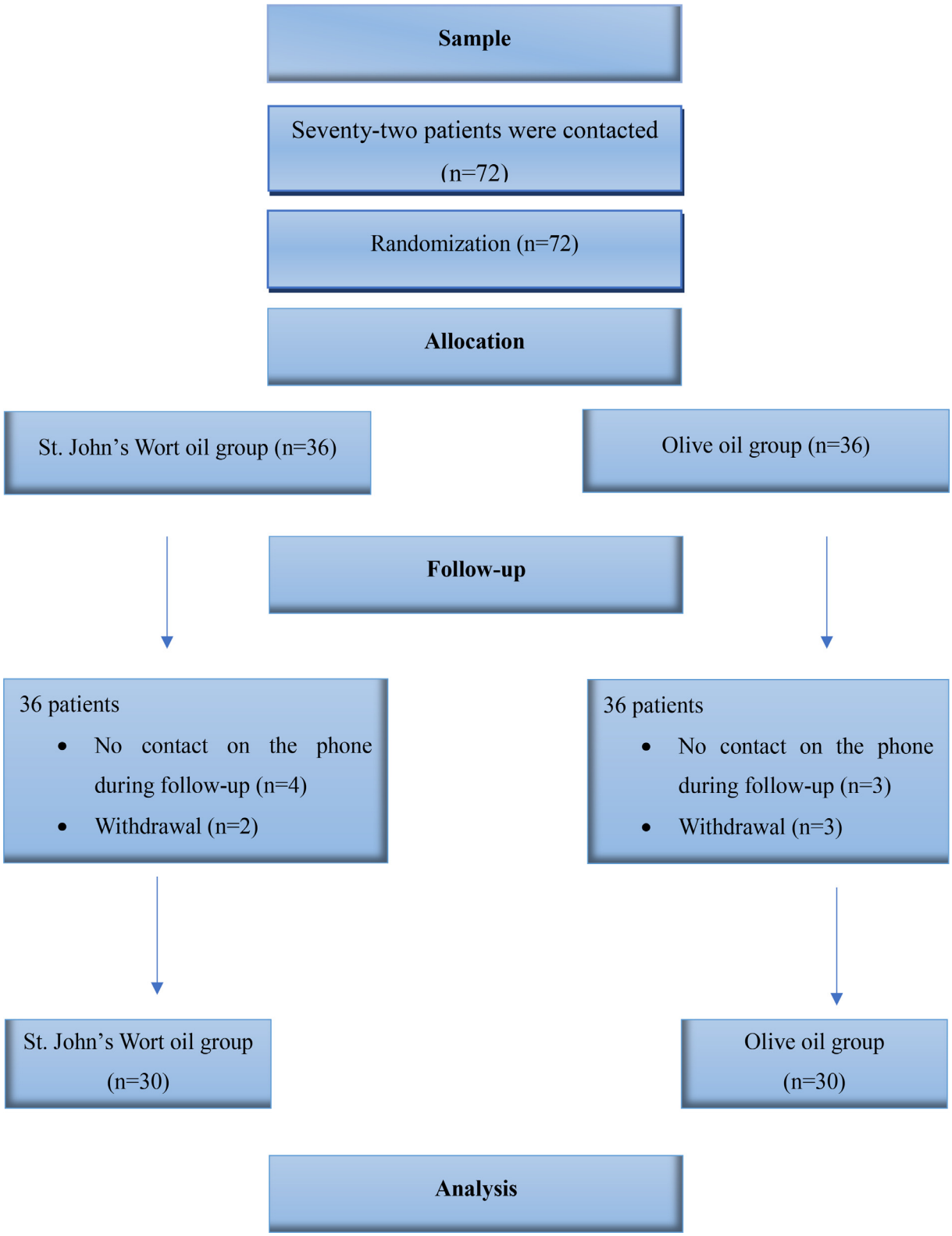

Figure 1. CONSORT flow chart.

were determined according to the physician's recommendation. All participants applied the oils themselves or had their family members apply them on their knees locally three times a day (morning, noon, and evening). The researcher called each participant once a day and asked them whether they applied the oil or not, how many painkillers they took, and whether they recorded that information on the chart. The researcher also reminded them to apply the oil if they did not. The researcher visited each participant at home at the end of the first and second weeks and administered the VAS. At the end of 3 weeks, the researcher invited the partic-

OİL TREATMENTS PROTOCOL
1. Prepare the materials (such as oil, gloves, cleaning wipes).
2. To practice, choose a quiet, dimly lit room and a place where you can lie down comfortably.
3. Wash your hands.
4. Open your knee area. If there is visible pollution in the area where the procedure will be performed, ensure its cleaning.
5. Take some oil in your hand and apply the oil to the front, side and back of the knee, covering at least 10 cm above and below.
6. Do not take a bath or wash the application area for two hours after the application.
7. Protect the area from the sun during the three weeks of application.
8. Do the application three times a day (morning, noon and evening), at the same time.
9. Continue the application every day of the week for three weeks (21 days).
10. After performing the application, put a mark (+) on the patient follow-up chart indicating that the application has been completed.
11. Record in the Application and Patient Monitoring Chart whether you took any painkillers during the day, and if so, at what time.

Figure 2. Oil treatments protocol.

ipants to the clinic and administered the VAS and WOMAC again. Each participant filled out the VAS four times: at the beginning of the intervention and the first, second, and third weeks of the intervention. They filled out the WOMAC twice: at the beginning and end of the interventions.

Outcome Measures

Patient identification form

The patient identification form was based on a literature review conducted by the researcher (Barthel et al., 2009; Kooshki et al., 2016). The form consisted of 23 items on age, sex, occupation, diagnosis, diseases, medications, etc.

WOMAC scale

The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) is a health status scale assessing osteoarthritis-related disability. WOMAC was developed (1982) and revised (1998) by Bellamy et al (Kooshki et al., 2016). The index consists of 24 items rated on a five-point Likert-type scale. The index has three subscales: pain (five items), stiffness (two items), and physical function (17 items). The total score of the "pain" subscale ranges from 0-20. The total score of the "stiffness" subscale ranges from 0-8. The total score of the "physical function" subscale ranges from 0-68. Higher scores indicate more symptoms and physical limitations (Cheung et al., 2017). The index was adapted into Turkish by Tüzün et al. (2005) (Tüzün et al., 2005). The Turkish version has a Cronbach's alpha of 0.70. WOMAC-pain, stiffness, and physical function subscales had Cronbach's alpha values of 0.71, 0.90, and 0.93, respectively, before the intervention. They had Cronbach's alpha values of 0.91, 0.87, and 0.97, respectively, after the intervention. The total scale had a Cronbach's alpha of 0.94 and 0.97 before and after the intervention, respectively.

Visual analog scale

The Visual Analog Scale is used to convert some values that cannot be measured numerically into numbers. The VAS is a 10 cm long horizontal or vertical line with anchor statements "no pain or pain at its least" at the left-most end and "unbearable pain or worst pain imaginable" at the right-most end. The participant marks a point on the line that best represents their pain level (Price et al., 1983). The distance of the mark to the left end is measured with a ruler (Williamson & Hoggart, 2005).

Oil Treatment Protocols

The oil treatment protocols were based on a literature review and expert feedback (Nasiri et al., 2016; Tosun et al., 2017). The oil treatment protocol included these steps: (1) Prepare the materials (such as oil, gloves, cleaning wipes); (2) to practice, choose a quiet, dimly lit room and a place where you can lie down comfortably; (3) wash your hands; and (4) open your knee area. If the area where the procedure will be performed is visibly dirty, clean it; (5) take some oil in your hand and apply the oil to the front, side, and back of the knee, covering at least 10 cm above and below; (6) do not take a bath or wash the application area for 2 hours after the application; (7) protect the area from the sun during the 3 weeks of application; (8) do the application three times a day (morning, noon and evening), at the same time; (9) continue the application every day of the week for 3 weeks (21 days); (10) after performing the application, put a mark (+) on the patient follow-up chart indicating that the application has been completed; (11) record in the Application and Patient Monitoring Chart whether you took any painkillers during the day, and if so, at what time.

Participants were treated with St. John's Wort oil (experimental group) or olive oil (control group). St. John's Wort oil is obtained by keeping the flowering parts of the plant in olive oil under the sun for 15 days. This is why the control group participants were treated with olive oil. Olive oil and St. John's Wort oil were supplied from *Helvacızade Gıda İlaç Kimya* according to their specifications. The research was financially supported by the Scientific Research Projects Coordination Office of Erciyes University, and the oils used were purchased with this support.

Sample Size Calculation

During data collection, we made an interim evaluation based on the data of the sample. A power analysis was conducted. The results showed that the sample was large enough to detect significant differences. Therefore, 60 patients were recruited and divided into intervention ($n = 30$) and control ($n = 30$) groups. The data were analyzed using Turcosa Cloud at a significance level of 0.05. The VAS had a power of 0.89, while the WOMAC-pain, WOMAC-stiffness, and WOMAC-physical function subscales had a power of 0.91, 0.87, and 0.97, respectively.

Statistical Analysis

The data were analyzed using descriptive and content analysis on NVIVO. The quantitative data were analyzed using Turcosa Cloud (Turcosa Ltd Co). The independent variables were sociodemographic characteristics (age, gender, education, etc.). The dependent variables were VAS and WOMAC scores. Number (n), percentage (%), mean ± standard deviation, median (M), first quarter (Q1), and third quarter (Q3), [M (Q_1 – Q_3)] values were used for descriptive statistics. Histograms, q-q plots, and the Shapiro-Wilk test were used for normality testing. Group variances were determined using Levene's test. The assumption of sphericity was evaluated using the Mauchly test. Two-way repeated measures analysis of variance (2-way RM analysis of variance) was used to determine the effect of group and time on VAS and WOMAC scores. Independent two-sample *t* test and Man-Whitney *U* test were used to compare paired groups. Paired *t* test and repeated measures analysis of variance (RM analysis of variance) were used to measure the scale scores over time. The exact method of the χ^2 test was used for intergroup comparisons of categorical variables. Power analysis was performed to determine the power of the study; $p < .05$ was considered statistically significant in comparisons.

Ethical Considerations

The study was approved by the Clinical Research Ethics Committee of a university (date: 08/11/2016; No: 2016/586; clinicaltrials.gov id: NCT0566399). Permission was obtained from the hospital. Informed consent was obtained from all participants. The study was conducted according to the ethical principles outlined by the World Medical Association's Declaration of Helsinki.

Side Effects

Participants had no side effects and no negative feedback.

Results

Quantitative Results

Table 1 shows the participants' descriptive characteristics. The experimental and control groups had similar sociodemographic characteristics ($p>.05$). Table 2 shows the participants' osteoarthritis-related characteristics. The groups had similar

Table 1
Sociodemographic Characteristics.

		Experimental Group (n =30)	Placebo Control Group (n = 30)	***p***
Age (y)		60.06 ± 11.53	58.56 ± 10.45	.624[a]
Gender, n (%)	Woman	20 (66.7)	21 (70.0)	.781[b]
	Man	10 (33.3)	9 (30.0)	
Education (degree)	Literate	7 (23.3)	7 (23.3)	.418[b]
	Primary school	15 (50.0)	20 (66.7)	
	Middle school	2 (6.7)	1 (3,3)	
	High school or higher	6 (20.0)	2 (6.7)	
Occupation	Housewife	17 (56.7)	20 (66.7)	.766[b]
	Retired	8 (26.7)	5 (16.7)	
	Farmer	2 (6.6)	3 (10.0)	
	Worker/employee/self-employed	3 (10.0)	2 (6.7)	
Marital Status	Married	28 (93.3)	28 (93.3)	.999[b]
	Single	2 (6.7)	2 (6.7)	
BMI	Underweight	2 (6.7)	2 (6.7)	.503[b]
	Normal	7 (23.3)	9 (30.0)	
	Overweight	11 (36.7)	14 (46.7)	
	Obese	10 (33.3)	5 (16.6)	
Regular exercise	Yes	4 (13.3)	5 (16.7)	.999[b]
	No	26 (86.7)	25 (3.3)	
Climbing stairs at home	Yes	22 (73.3)	15 (50.0)	.063[b]
	No	8 (26.7)	15 (50.0)	
Using a support Device for walking	Yes	5 (16.7)	4 (13.3)	.999[b]
	No	25 (83.3)	26 (86.7)	
Performing the salaat	Yes	29 (96.7)	28 (93.3)	.999[b]
	No	1 (3.3)	2 (6.7)	
		n = 29	*n = 28*	
Salaat position [c]	Standing	9 (31.0)	8 (28.6)	.839[b]
	Sitting	20 (69.0)	20 (71.4)	

[a] χ^2 test.
[b] Independent samples t test.
[c] [c]Percentages are based on n.

Table 2
Disease-related Characteristics.

		Experimental Group (n = 30)	Placebo Control Group (n = 30)	*p*
Having had knee pain for a year	≤1	6 (20.0)	9 (30.0)	.485[a]
	2-3	14 (46.7)	11 (36.7)	
	4-5	7 (23.3)	4 (13.3)	
	6≥	3 (10.0)	6 (20.0)	
Diagnosis (year)	1-3	21 (70.0)	23 (76.7)	.901[a]
	4-6	7 (23.3)	5 (16.6)	
	6≥	2 (6.7)	2 (6.7)	
Duration of knee pain in the past month	Intermittent/increasing with movement/ increasing in recent days	4 (13.3)	3 (10.0)	.999[a]
	Every day/all the time	26 (86.7)	27 (90.0)	
Taking OA medication regularly	Yes	10 (33.3)	5 (16.7)	**.028**[a]
	No	20 (66.7)	25 (83.3)	
Having a chronic disease other than OA	Yes	20 (66.7)	23 (76.7)	.390[a]
	No	10 (33.3)	7 (23.3)	
Medication used regularly	Yes	18 (60.0)	22 (73.3)	.273[a]
	No	12 (40.0)	8 (26.7)	

[a] Independent samples t test/Mann-Whitney U test.OA = Osteoarthritis

osteoarthritis-related characteristics, except for regular osteoarthritis medication use.

Table 3 shows the VAS scores of the groups. The groups had similar VAS scores at the beginning (first follow-up) and the end of the first week (second follow-up; $p > .05$). However, there was a significant difference in the mean VAS scores at the end of the third week (fourth follow-up; $p < .05$). The experimental group had a mean VAS score of 5.90 ± 1.09 and 2.43 ± 1.30 in the first and fourth follow-up, respectively. The control group had a mean VAS score of 5.87 ± 1.14 and 4.33 ±1 .49 in the first and fourth follow-up, respectively. The VAS scores decreased significantly ($p<.05$). However, the mean VAS score decreased two-fold in the experimental group compared with the control group ($p<.05$).

Table 4 shows the participants' WOMAC scores before and after the interventions. There was a significant difference in preintervention WOMAC-pain scores between the experimental and con-

Table 3
Comparison of the VAS Pain Scale Scores of the Intervention and Placebo Control Groups According to the Follow-ups.

		Experimental Group (n=30) ($\bar{x}\pm ss$)	Placebo Control Group (n=30) ($\bar{x}\pm ss$)	$p^{\#}$
Follow-ups	Baseline (1. Follow-up)	5.90±1.09[a]	5.87±1.14[a]	0.908
	First week (2. Follow-up)	5.03±1.16[b]	5.43±1.14[b]	0.182
	Second week (3. Follow-up)	4.07±1.11[c]	4.90±1.30[c]	**0.010**
	Third week (4. Follow-up)	2.43±1.30[d]	4.33±1.49[d]	**<0.001**
	Difference (VAS1-VAS4)	3.0 (2.8-4.0)	1.5 (1.0-2.0)	**<0.001**
	p^{*}	**<0.001**	**<0.001**	

Test power: 0.035
The same letters in the same column indicate similarity between times, while different letters indicate differences between times.
p*: Indicates significance across time.
p#: Indicates significance between groups.
SD: Standard deviation.
VAS: Visual Analog Scale

Table 4
Comparison of the WOMAC Scale Sub-dimension Scores of the Intervention and Placebo Control Groups Before and After the Application.

WOMAC Scale Sub-dimension		Experimental Group (n = 30) ($\bar{x}$ ± SD)	Placebo Control Group (n = 30) ($\bar{x}$ ± SD)	p
Pain	Before the intervention	12.90 ± 3.40	11.00 ± 2.85	**.022**
	After the intervention	7.03 ± 4.18	9.90 ± 4.44	**.013**
	Difference	5.87 ± 4.44	−1.10 ± 3.90	**<.001**
	p	**<0.001**	0.133	
Stiffness	Before the intervention	4.67 ± 2.48	4.57 ± 1.85	.860
	After the intervention	2.07 ± 1.95	3.90 ± 1.67	**<.001**
	Difference	2.60 ± 2.76	−0.67 ± 2.06	**.003**
	p	**<0.001**	0.086	
Physical function	Before the intervention	36.67 ± 14.09	35.07 ± 9.16	.604
	After the intervention	20.50 ± 13.65	31.07 ± 12.48	**.003**
	Difference	16.17 ± 15.09	−4.00 ± 10.77	**.001**
	p	**.001**	.051	

Test power: <0.01.
SD = Standard Deviation; WOMAC = Western Ontario and McMaster Universities Osteoarthritis.

trol groups ($p < .05$). However, there was no significant difference in preintervention WOMAC-stiffness and WOMAC-physical function scores between them ($p > .05$). The experimental group had significantly low WOMAC-pain, WOMAC-stiffness, and WOMAC-physical function subscale scores after the interventions than before the interventions ($p < .05$). The control group had low WOMAC-pain, WOMAC-stiffness, and WOMAC-physical function subscale scores after the interventions than before the interventions. However, the difference was statistically insignificant ($p > .05$). The experimental group had significantly lower WOMAC-pain, WOMAC-stiffness, and WOMAC-physical function subscale scores than the control group ($p < .05$).

Half the experimental group participants did not use any painkillers during the intervention (50%), while less than half of the control group participants did not use any painkillers during the intervention (23.3%). The difference between the groups was statistically significant ($p < .05$). The control group participants used significantly more painkillers than the experimental group participants.

Qualitative Results

In-depth interviews were conducted to determine the participants' pain experiences and their opinions about the oil they use. These interviews were held twice with each participant separately, in a quiet room at the hospital, lasting approximately 15-20 minutes, before the application and at the end of the 3-week application. In the first interview, the researcher asked the participants to describe their knee pain, what difficulties they encountered with pain in daily life, and what they did to overcome the pain they experienced, other than taking painkillers. In the last interview, questions were asked about the effect of the oil used. Six themes emerged from the responses. These were discussed under the headings of "pain-related experiences," "the effect of pain on daily life," and "nondrug applications to relieve pain," "the effect of the oil used on knee pain," "the effect of the oil used on knee stiffness," and "the easy and difficult parts of oil application."

Theme 1: Views about pain

Before the interventions, participants stated that they felt pain when bending their knees, sitting and standing up, performing the salaat (this is a form of worship), and sitting on their knees. The following are some quotations:

> *"I feel a lot of pain when I bend my knee and when I climb up and down the stairs. I have to climb up the stairs."* (P1, F, 48, experimental).

> *"Of course, it limits my daily life. Like, let's say I have to do something, and so I stand up, and that is when I feel pain. I lean on my walking stick. But which side am I supposed to lean? I mean, when I lean on my right, I feel pain in my knee, but when I lean on my left, I feel like my heart is heavy."* (P7, M, 61, experimental).

> *"It hurts when I stretch my legs out; it hurts when I pull them in. I feel pain when I climb up the stairs. I feel pain when I walk up a hill. I feel like it is breaking."* (Mrs. Y. K., 55, control).

> "*I cannot get any sleep because of the pain. So, I have to take painkillers. I mean, it is like it is pinching. I am OK when I walk. I mean, it does not hurt. It is not like I can walk very fast anyway. I just walk at my own pace.*" (P21, F, 72, control).

Theme 2: The effect of pain on daily life

Before the interventions, participants noted that their pain affected their daily lives adversely. They stated that they felt pain when getting up in the morning, climbing up and down the stairs, getting on and off the toilet, performing the salaat, and standing or walking for a long time. The following are some quotations:

> *"I have a hard time getting up. I need to get some support with my hand to do it. Or when I perform the salaat. I sometimes climb up the stairs one by one."* (P2, M, 50, experimental).

> "*I quit performing the salaat. I just could not do it (because it hurt). I used to do house chores. I used to graze my animals…But not anymore, because of my knee. I cannot stay indoors, I mean, I just cannot.*" (P40, F,53, experimental).

> "*I have a hard time making some moves when I take a walk. I have a hard time going to the mosque and performing the salaat.*" (P42, M, 75, control).

> "*I am on my own. There are too many things I have to do standing up. So, I am always up on my two feet. I perform the salaat sitting. I have a hard time going to the toilet, too*." (P43, F, 63, control).

Theme 3: Practices for pain relief

The researcher asked all participants whether they had done anything special to relieve their pain, except for what was recommended by their doctors. He also asked them whether whatever they did worked. Most participants stated that they had not done anything special to relieve the pain they had. Some participants noted that they had tried some herbal products. Some of them said that those herbal products did not work, while others stated that they did not know whether herbal products worked because they had not used them regularly. The following are some quotations:

> *"I would rubbed ozone oil on my knee. I did it last summer, but it did not work. I get by with painkillers. I take some painkillers and take a little walk. But if I do not take painkillers, I feel like I am crippled. I've been on all kinds of painkillers. I used black oil, black cumin oil, and whatnot. That is how it is.*" (P34, F, 79, experimental).

> *"Of course, I tried some other methods, like herbal medicine or something. We concocted some stuff and rubbed it on my knee. They worked for a while, but nothing permanent*." (P6, F,45, experimental).

> "*Yes, I had rubbed some stuff on my knee. I rubbed some black cumin oil, nothing else. I' have never been on any medication. I only took it once, but people said it was dangerous. I mean, a muscle relaxant. It helps me climb up and down and move around. I can do those things until it fades out…If that is possible, I need something that will heal me for good."* (P24, F, 73, control).

> "*I rubbed some black cumin oil once. It did not do me any good. I use the creams the doctor prescribed. None of them worked. They relieve some of my pain. But it just comes back*." (P46, F, 51, control).

Theme 4: The effect of oil on knee pain

The VAS and WOMAC scores showed that St. John's Wort oil helped the experimental group participants feel less pain (Table 4). Participants' statements confirmed the quantitative results. Most experimental group participants stated that St. John's Wort oil relieved their pain and made their knees more flexible. The following are some quotations:

> "*It relieved the pain. It kicked in after day 5. I mean, I think it worked, compared to the pain I had before…*" (P31, F, 50, experimental).

> "*I think it worked out. I feel a bit more comfortable now. I think it might take all the pain away for good if I keep using it. My left knee used to hurt more than my right knee. Now, it is the other way around. So, I first rubbed the oil on my left knee and then what is left on my right knee*." (P8, M, 71, experimental).

> "*Yes, I think so. My knee used to be stiffer, and now it is more flexible. There is a one hundred percent difference*." (P37, M, 47, experimental).

Some control group participants noted that the olive oil did them some good, whereas others stated that it did not work at all. The quantitative results showed that the control group participants had a significantly lower mean VAS score after the intervention than before it (Table 3). The following are some quotations:

> *"Yes, I think it worked. It did me some good. I feel much more comfortable. It made the veins more flexible. Now I feel fine, very fine."* (P49, F, 48, control).

> *"Yes, I believe it worked out. I mean, it softened that region. I can move my knee much more now. And I have no pain. I used to have a hard time going out and performing the salaat, but not anymore."* (P44, F, 55, control).

On the other hand, some control group participants noted that the olive oil was not much helpful. The following are some quotations:

> *"Yes, it did some good, to some extent. It made my knee softer. But, I still have some pain."* (P51, F. 63, control).

> *"No, it did not work at all, not at all, son."* (P21, F, 72, control).

> "*Yes, a little, it helped just a little. It did me some good the first time I rubbed it, but after that, it did not help me at all*." (P41, F, 50, control).

Theme 5: The effect of oil on knee stiffness.

The experimental group participants had a significantly lower mean WOMAC-stiffness subscale score after the intervention than before it (Table 4). The qualitative results confirmed this.

The experimental group participants stated that St. John's Wort oil softened their knees and resulted in less convulsion. The following are some quotations:

> *"It helped me a lot. It softened my knee, like a lot. So, it worked out. Before, it was too stiff."* (P55, F, 60, experimental).

> *"It opened up my veins a lot. It is much less stiff now. I can say 90%. I mean, it helped me with the vein stiffness. I cannot say the same thing for the pain, but it really did some good about the stiffness."* (P31, F, 50, experimental).

> *"I have less stiffness on my knees. It softened my knees."* (P47, F, 45, experimental).

> *"It softened my knees a little, I mean a little. It makes my knee more flexible when I rub it."* (P34, F, 79, experimental).

> *"Yes, it helps. My knees turn into cotton when I rub it on them, and they get strained when I do not. It softens my knees when I rub it on them."* (P39, F, 63, experimental).

Some control group participants noted that the olive oil helped with the stiffness, whereas others noted that it did not. The following are some quotations:

> *"There is this thing, like, there used to be some sort of sound coming from my cartilages, now there is less sound. There used to be some crackling and cracking, but now it is much less. I used to hear that crackling every time I moved my knee. Now, I get it a*

little when I sit down and stand up. I mean, I think it worked because it made my knees softer." (Mr. R.K., 58, control).

"When I move my knee like this, it makes a crackling sound. When I go like this, I feel the stiffness. So, it did not work out." (P19, F, 55, control).

"No, it did not do me any good." (P26, M, 76, control).

Theme 6: The easy and challenging parts of the intervention

The researchers asked all participants about the easy and challenging parts of the interventions. Most participants stated that the interventions were easy as they had no difficulty applying them by themselves. The following are some quotations:

"*It is not that hard, as long as I am home. I have no difficulty applying the oil as long as I am not going out*." (P57, M, 52, experimental).

"It was easy. I had no problem at all. I even enjoyed it. I rubbed the oil all over my knee…" (P39, F, 63, experimental).

"I had no difficulty rubbing the oil over my knee. But I could not get up before I made some moves. And I could not step on my foot. My knee was working slowly." (P24, F, 73, control).

"*It is very easy, there is nothing hard about it. I just rubbed it like this and wrapped it with a plastic wrap to contain it*." (P25, F, 53, control).

Some control group participants stated that rubbing the olive oil was a bit hard as they had difficulty keeping it clean. The following are some quotations:

"*It was a bit of a hassle. I mean, I had to wrap it with a paper towel. And I did not want to wipe it off to keep the oil over my knee. So, this was a bit hard*." (P59, F., 55, control).

"It is not hard at all, but I needed to wait until the skin absorbed the oil. I mean, I did not want it all over my jeans. This was the only difficulty." (P60 M, 37, control).

"It is not hard, but I had to cover it with something when I rubbed it during the day, I had to contain the oil. There is no other way. You have to cover it with something. You cannot just rub it and go. You have to cover it with a plastic bag or something. But I do not like that." (P30 F, 70, control).

Discussion

This study investigated the effect of St. John's Wort oil on pain intensity and physical functions in people with knee osteoarthritis. The experimental group had significantly lower VAS scores at the end of the third and fourth weeks than the control group. The experimental group had significantly lower WOMAC-pain, WOMAC-stiffness, and WOMAC-physical function subscale scores at the end of the intervention than the control group. Analgesics such as nonsteroidal anti-inflammatory drugs (NSAIDs) used to relieve pain in osteoarthritis have gastrointestinal side effects and dose-dependent effects (Xu et al., 2017). Therefore, more and more people turn to integrative medical methods for the relief of symptoms related to knee osteoarthritis (Wang et al., 2016). Exercise, herbal treatments, aromatherapy, massage, physical therapy, hot and cold applications, acupuncture, acupressure, or Tai Chi are used to reduce osteoarthritis-related pain and improve function (Cheung et al., 2017; Karadağ et al., 2019; Nahin et al., 2016; Wang et al., 2016). Although people use the oil-soluble extract of St. John's Wort as a painkiller or as an antirheumatic drug (Kalaba et al., 2015), we know little about its analgesic properties. To our knowledge, there is no research investigating the effect of St. John's Wort on osteoarthritis-related pain. However, some researchers have conducted randomized controlled trials to investigate the effect of different products on osteoarthritis-related pain (Efe Arslan et al., 2019; Kooshki et al., 2016; Nasiri et al., 2016; Shakouri et al., 2018).

Jamadi et al. (2019) conducted a randomized placebo trial to investigate the effect of curcumin ointment on knee pain in older adults with osteoarthritis and found that the ointment significantly reduced osteoarthritis-related pain (Jamadi et al., 2019). Tuna et al. (2018) divided 60 geriatric people with osteoarthritis into experimental (n = 30) and control (n = 30) groups to investigate the effect of black cumin oil on pain. They reported that the experimental group had a significantly lower mean VAS score than the control group, suggesting that black cumin oil is effective in reducing osteoarthritis-related pain (Tuna et al., 2018). Tosun et al. (2017) performed an experimental study to investigate the effect of self-knee massage with ginger oil in patients with osteoarthritis. They determined that self-massage with ginger oil could be used as a complementary method to reduce osteoarthritis-related pain and improve functionality in activities of daily living (Tosun et al., 2017). Nasiri et al. (2016) undertook a randomized controlled clinical trial to determine the effect of aromatherapy massage with lavender essential oil on pain in patients with knee osteoarthritis. They randomized 90 patients into intervention (aromatherapy massage with lavender essential oil), placebo (massage with almond oil), and control (without massage) groups. They reported that the experimental group had significantly lower mean VAS scores immediately after the intervention and 1 week after the intervention than the other groups. However, the researchers did not detect a significant difference in the VAS scores between the groups at the end of the fourth week (Nasiri et al., 2016). Nasiri and Mahmodi (2018) conducted a randomized controlled clinical trial to investigate the effect of aromatherapy massage and lavender essential oil on the activities of daily living of patients with knee osteoarthritis. They randomly assigned 90 patients into three groups: experimental group (aromatherapy massage with lavender essential oil), placebo group (massage with almond oil), and control group (without massage). The researchers observed a significant reduction in WOMAC scores immediately after the intervention and 1 week after the intervention. However, they did not detect a significant difference in WOMAC scores between the groups at the end of the fourth week (Nasiri & Mahmodi, 2018). Kooshki et al. (2016) conducted a crossover clinical trial to determine the effect of black cumin oil and oral acetaminophen on pain in older adults with knee osteoarthritis. They found that although both black cumin oil and oral acetaminophen helped reduce pain, the former was more effective than the latter (Kooshki et al., 2016). Efe Arslan et al. (2019) investigated the effect of aromatherapy massage on knee pain and functional status in patients with osteoarthritis. They randomized 95 patients into intervention (n = 33; aromatherapy massage), placebo (n = 30; conventional massage), and control (n = 32) groups. They found that the experimental group had significantly lower VAS scores than the other groups. They also reported that the experimental group had significantly lower WOMAC-pain, WOMAC-stiffness, and WOMAC-physical function subscale scores at the end of the first, second, and third weeks than the other groups (Efe Arslan et al., 2019). Pehlivan and Karadakovan (2019) investigated the effect of aromatherapy massage on pain, functional state, and quality of life in older adults with knee osteoarthritis. They randomized 90 participants into aromatherapy, massage, and control groups. They documented that the aromatherapy group had significantly lower WOMAC-pain, WOMAC-stiffness, and WOMAC-physical function subscale scores in the fourth and eighth weeks than the massage and control groups (Pehlivan & Karadakovan, 2019). Our experimental group

participants reported less pain and stiffness and more physical functioning over the weeks. Their VAS and WOMAC scores also supported this finding. Participants did not report any side effects. Although paracetamol and NSAIDs are used as analgesics to relieve pain and improve physical functions in osteoarthritis treatment, they have various side effects (Çelik et al., 2021; Conaghan et al., 2019). Our results also showed that the experimental group participants used significantly fewer painkillers than the control group participants. Our qualitative findings are consistent with this result.

The control group participants had a significantly lower mean VAS score in the last week than in the first week (Table 3). Although participants' WOMAC scores decreased as the weeks passed by, it was statistically insignificant (Table 4). Participants noted that olive oil reduced their pain and stiffness. However, there is limited research investigating the effect of olives and their derivatives on osteoarthritis. Some of them are animal studies, and some of them are human studies (Chin & Pang, 2017). Although olives can potentially prevent osteoarthritis-related cartilage damage thanks to their antioxidant and anti-inflammatory properties, more research is warranted on this topic (Chin & Pang, 2017). Nakhostin-Roohi et al. (2016) conducted a double-blinded randomized clinical trial to compare the effect of virgin olive oil and piroxicam phonophoresis on exercise-induced anterior knee pain. They randomized 93 patients into olive oil ($n = 31$), piroxicam ($n = 31$), and base gel phonophoresis ($n = 31$) groups. They reported that although all interventions were effective, olive oil worked faster than piroxicam or base gel phonophoresis (Nakhostin-Roohi et al., 2016).

Our participants also stated that they felt pain when performing activities of daily living, such as performing the salaat, doing chores, walking, etc. Some participants noted that they used alternative medicines to relieve knee pain, such as black cumin oil, ozone oil, cream, etc. However, none of the participants used those products regularly. The experimental group participants stated that St. John's Wort oil was effective in relieving their knee pain. Although some control group participants noted that olive oil was effective, some others remarked that it was not helpful at all. The experimental group participants also noted that St. John's Wort reduced their stiffness. Both St. John's Wort and olive oil application were easy for most participants. However, some participants had hygiene-related concerns.

Limitations

There are three important limiting factors in our study. First, patients continued to take analgesics throughout the study. Secondly, the participants were told the name of the oil they would use. Thirdly, the researcher could not observe the patients while performing the application.

Conclusions

St. John's Wort oil applied locally three times a day for 3 weeks reduces knee pain and stiffness and improves physical functioning in patients with knee osteoarthritis. Our quantitative results are consistent with our qualitative results. Applying St. John's Wort oil is an easy-to-use treatment with no side effects. Our participants stated that they wanted to keep using St. John's Wort oil to relieve their pain and stiffness. Healthcare professionals should have adequate knowledge about integrative medicine methods and encourage their patients to use St. John's Wort oil in addition to their current treatments. St. John's Wort oil reduces knee pain and stiffness and improves physical functioning in patients with knee osteoarthritis. However, further randomized single and double-blind trials are warranted to better understand the effect of St. John's Wort oil on pain, stiffness, and physical functions.

Clinical Implications

St. John's wort oil is popularly obtained by soaking St. John's wort flowers in olive oil. It can also be easily found in herbalists. St. John's wort oil is cheap and easy to apply and has no side effects when applied topically. Used topically, it is effective in relieving knee pain and helping patients become more physically active. For this reason, St. John's wort oil can be used topically for medical purposes in people with knee osteoarthritis. Nurses can play important roles in the use of St. John's wort oil for knee pain, performing the application in line with the doctor's request or knowledge, creating and developing clinical practice protocols, and guiding patients on how to obtain St. John's wort oil.

Declaration of competing interest

The authors declared that they have no conflict of interest.

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References

Al-Omari, B., & Hill, B. (2020). Nursing people with osteoarthritis. *British Journal of Nursing, 29*(18), 1060–1063.

Allen, K. D., Thoma, L. M., & Golightly, Y. M. (2022). Epidemiology of osteoarthritis. *Osteoarthritis and Cartilage, 30*(2), 184–195.

Aşçı, A., Baydar, T., & Şahin, G. (2007). Evaluation of usage of herbal preparation and drug interactions in elderly people from toxicological aspect. *Turkish Journal of Geriatrics, 10*(4), 203–214.

Assiri, K., Alyami, Y., Uyanık, J., & Romero-Reyes, M. (2017). Hypericum perforatum (St. John's Wort) as a possible therapeutic alternative for the management of trigeminal neuralgia (TN) A case report. *Complementary Therapies in Medicine, 30*, 36–39.

Aynaoğlu Hakverdi, Ö., & Önder, A. (2022). Kas İskelet Sistemi Rahatsizliklarinda Kullanılan Bitkisel Droglar. *Bütünleyici ve Anadolu Tıbbı Dergisi, 3*(February), 31–50.

Barthel, R. H., Haselwood, D., Longley, S., Gold, M. S., & Altman, R. D. (2009). Randomized controlled trial of diclofenac sodium gel in knee osteoarthritis. *Seminars in Arthritis and Rheumatism, 39*, 203–212.

Bukhari, I. A., Dar, A., & Khan, R. (2004). Antinociceptive activity of methanolic extracts of St. John's Wort (Hypericum perforatum) preparation. *Pakistan Journal Of Pharmaceutical Sciences, 17*(2), 13–22.

Çelik, M., Çelik, S. T., & Tetik, B. K. (2021). Approach to knee osteoarthritis in the primary care with current guidelines. *Ankara Medical Journal, 21*(2), 304–316.

Cheung, C., Wyman, J. F., Bronas, U., McCarthy, T., Rudser, K., & Mathiason, M. A. (2017). Managing knee osteoarthritis with yoga or aerobic/strengthening exercise programs in older adults: a pilot randomized controlled trial. *Rheumatology International, 37*(3), 389–398.

Chin, K. Y., & Pang, K. L. (2017). Therapeutic effects of olive and its derivatives on osteoarthritis: From bench to bedside. *Nutrients, 9*(10), 1–18.

Conaghan, P. G., Arden, N., Avouac, B., Migliore, A., & Rizzoli, R. (2019). Safety of paracetamol in osteoarthritis: What does the literature say? *Drugs and Aging, 36*(s1), 7–14.

Cui, A., Li, H., Wang, D., Zhong, J., Chen, Y., & Lu, H. (2020). Global, regional prevalence, incidence and risk factors of knee osteoarthritis in population-based studies. *EClinicalMedicine, 29-30*, Article 100587.

Efe Arslan, D., Kutlutürkan, S., & Korkmaz, M. (2019). The effect of aromatherapy massage on knee pain and functional status in participants with osteoarthritis. *Pain Mechanisms and Management, 20*(1), 62–69.

Evaniew, A. L., & Evaniew, N. (2017). Knee osteoarthritis: Therapeutic alternatives in primary care. *World Journal of Orthopedics, 8*(2), 187–191.

Galeotti, N., & Ghelardini, C. (2013). St. John's wort reversal of meningeal nociception: A natural therapeutic perspective for migraine pain. *Phytomedicine, 20*(10), 930–938.
Galeotti, N., Maidecchi, A., Mattoli, L., Burico, M., & Ghelardini, C. (2014). St. John's Wort seed and feverfew flower extracts relieve painful diabetic neuropathy in a rat model of diabetes. *Fitoterapia, 92*, 23–33.
Galeotti, N., Vivoli, E., Bilia, A. R., Vincieri, F. F., & Ghelardini, C. (2010). St. John's Wort reduces neuropathic pain through a hypericin-mediated inhibition of the protein kinase C γ and ε activity. *Biochemical Pharmacology, 79*(9), 1327–1336.
Galeottti, N., Mersedeh, F., Bianchi, E., & Ghelardini, C. (2014). PKC-mediated potentiation of morphine analgesia by St. John's wort in rodents and humans. *Journal of Pharmacological Sciences, 124*(4), 409–417.
Huang, Z., Ding, C., T, L., & Yu, S (2018). Current status and future prospects for disease modification in osteoarthritis. *Rheumatology, 57*, 108–123.
Jamadi, N., Adib-Hajbaghery, M., & Soleimani, A. (2019). The effect of Curcumin ointment on knee pain and quality of life in older adults with osteoarthritis. *BMC Complementary Medicine and Therapies, 20*(1), 305.
Jarić, S., Popović, Z., Mačukanović-Jocić, M., Djurdjević, L., Mijatović, M., Karadžić, B., Mitrović, M., & Pavlović, P. (2007). An ethnobotanical study on the usage of wild medicinal herbs from Kopaonik Mountain (Central Serbia). *Journal of Ethnopharmacology, 111*(1), 160–175.
Johne, A., Brockmöller, J., Bauer, S., Maurer, A., Langheinrich, M., & Roots, I. (1999). Pharmacoknetics and drug disposition, pharmacokinetic interaction of digoxin with an herbal extract from St John's wort. *Clinical Pharmacology & Therapeutics, 66*(4), 338–345.
Kalaba, V., Glušac, J., Stijepić, M., Kalaba, D., & Đurđević Milosević, D. (2015). Antimicrobial activity of hypericum perforatum essential oil. *Quality of Life, 12*(3-4), 45–52.
Karadağ, S., Taşci, S., Doğan, N., Demir, H., & Kiliç, Z. (2019). Application of heat and a home exercise program for pain and function levels in patients with knee osteoarthritis: A randomized controlled trial. *International Journal of Nursing Practice, 25*(5), 1–9.
Kooshki, A., Forouzan, R., Rakhshani, M. H., & Mohammadi, M. (2016). Effect of topical application of nigella sativa oil and oral acetaminophen on pain in elderly with knee osteoarthritis: A crossover clinical trial. *Electronic Physician, 8*(11), 3193–3197.
Magni, A., Agostoni, P., Bonezzi, C., Massazza, G., Menè, P., Savarino, V., & Fornasari, D. (2021). Management of osteoarthritis: Expert opinion on NSAIDs. *Pain and Therapy, 10*(2), 783–808.
Nahin, R. L., Boineau, R., Khalsa, P. S., Stussman, B. J., & Weber, W. J. (2016). Evidence-based evaluation of complementary health approaches for pain management in the United States. *Mayo Clinic Proceedings, 91*(9), 1292–1306.
Nakhostin-Roohi, B., Khoshkhahesh, F., & Bohlooli, S. (2016). Effect of virgin olive oil versus piroxicam phonophoresis on exercise-induced anterior knee pain. *Avicenna Journal of Phytomedicine, 6*(5), 535–541.
Nasiri, A., & Mahmodi, M. A. (2018). Aromatherapy massage with lavender essential oil and the prevention of disability in ADL in patients with osteoarthritis of the knee: A randomized controlled clinical trial. *Complementary Therapies in Clinical Practice, 30*, 116–121.
Nasiri, A., Mahmodi, M. A., & Nobakht, Z. (2016). Effect of aromatherapy massage with lavender essential oil on pain in patients with osteoarthritis of the knee: A randomized controlled clinical trial. *Complementary Therapies in Clinical Practice, 25*, 75–80.
Nowacki, L. C., Worfel, P. R., Martins, P. F. A., Santos, R. S., dos, Stechman-Neto, J., & de Souza, W. M. (2015). Analgesic effect of Hypericum perforatum, Valeriana officinalis and Piper methysticum for orofacial pain. *Brazilian Journal of Oral Sciences, 14*(1), 60–65.
Oliveira, A. I., Pinho, C., Sarmento, B., & Dias, A. C. P. (2016). Neuroprotective activity of hypericum perforatum and its major components. *Frontiers in Plant Science, 7*, 1–15.
Pehlivan, S., & Karadakovan, A. (2019). Effects of aromatherapy massage on pain, functional state, and quality of life in an elderly individual with knee osteoarthritis. *Japan Journal of Nursing Science, 16*(4), 450–458.
Price, D. D., McGrath, P. A., Rafii, A., & Buckingham, B. (1983). The validation of visual analogue scales as ratio scale measures for chronic and experimental pain. *Pain, 17*(1), 45–56.
Seferos, N., Petrokokkinos, L., Kotsiou, A., Rallis, G., & Tesseromatis, C. (2016). Hypericum perforatum L. treatment restored bone mass changes in swimming stressed rats. *Stomatologija Baltic Dental and Maxillofacial Journal, 18*(1), 9–13.
Shakouri, A., Adljouy, N., Balkani, S., Mohamadi, M., Hamishehkar, H., Abdolalizadeh, J., & Kazem Shakouri, S (2018). Effectiveness of topical gel of medical leech (Hirudo medicinalis) saliva extract on patients with knee osteoarthritis: A randomized clinical trial. *Complementary Therapies in Clinical Practice, 31*(2018), 352–359.
Stojanović, N., Radulović, N., Randjelović, P., & Laketić, D. (2016). Antinociceptive properties of St. John's Wort (hypericum perforatum) and other hypericum species. *Natural Product Communications, 11*(11), 1741–1747.
Tosun, B., Unal, N., Yigit, D., Can, N., Aslan, O., & Tunay, S. (2017). Effects of self-knee massage with ginger oil in patients with osteoarthritis: An experimental study. *Research and Theory for Nursing Practice, 31*(4), 379–392.
Tuna, H. I., Babadag, B., Ozkaraman, A., & Balci Alparslan, G. (2018). Investigation of the effect of black cumin oil on pain in osteoarthritis geriatric individuals. *Complementary Therapies in Clinical Practice, 31*(March), 290–294.
Tüzün, E. H., Eker, L., Aytar, A., Daşkapan, A., & Bayramoğlu, M. (2005). Acceptability, reliability, validity and responsiveness of the Turkish version of WOMAC osteoarthritis index. *Osteoarthritis and Cartilage, 13*(1), 28–33.
Uchida, S., Hirai, K., Hatanaka, J., Hanato, J., Umegaki, K., & Yamada, S. (2008). Antinociceptive effects of St. John's Wort, Harpagophytum procumbens extract and grape seed proanthocyanidins extract in mice. *Biological and Pharmaceutical Bulletin, 31*(2), 240–245.
Wang, C., Schmid, C. H., Iversen, M. D., Harvey, W. F., Fielding, R. A., Driban, J. B., Price, L. L., Wong, J. B., Reid, K. F., Rones, R., & McAlindon, T. (2016). Comparative effectiveness of Tai Chi versus physical therapy for knee osteoarthritis: A randomized trial. *Annals of Internal Medicine, 165*(2), 77–86.
Williamson, A., & Hoggart, B. (2005). Pain: A review of three commonly used pain rating scales. *Journal of Clinical Nursing, 14*(7), 798–804.
Wölfle, U., Seelinger, G., & Schempp, C. M. (2014). Topical application of St. John's Wort (Hypericum perforatum). *Planta Medica, 80*(2-3), 109–120.
Xu, Q., Chen, B., Wang, Y., Wang, X., Han, D., & Ding, D. (2017). The effectiveness of manual therapy for relieving pain, stiffness, and dysfunction in knee osteoarthritis: A systematic review and meta-analysis. *Pain Physician, 20*, 229–243.