

Effect of Jujube/Frankincense as supportive therapy to alleviate the pain with knee osteoarthritis

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Zizyphus jujuba is a thorny Rhamnaceae plant found throughout Europe and Southeast Asia. It possesses medicinal properties and is utilized in traditional medicine. Frankincense is recognized for its analgesic properties. The purpose of this study was to determine the anti-nociceptive efficacy of *Z. jujuba* and Frankincense in assessing their effect on pain associated with knee osteoarthritis. This research included 46 people ranging in age from 50 to 70 years. They were placed into two groups: test and control. *Z. jujuba* and Frankincense pills were made, and participants were given a Persian-validated Western Ontario and McMaster Universities (WOMAC), and visual analogue score (VAS) questionnaire. The variables were evaluated before and after the intervention. In the test group, there was a considerable decrease in pain VAS score following the administration of dosages of *Z. jujuba*/Frankincense pills. The analgesic efficacy of the aforementioned herbal medicines under study was significant after taking mixed jujube/frankincense/aloe vera tablets at doses of 250 mg/100 mg/25 mg, respectively. The combined standardized mean difference for the WOMAC, were 14.56 ± 3.2 , 13.9 ± 3.50 , and 13.33 ± 4.09 , for the before, one-week, and one-month follow-ups, respectively. WOMAC and VAS scores were different between “before intervention” as well as both “one week”, and “one-month” follow-ups. In summary, pain reduced in study group compared to their respective baseline (VAS and WOMAC outcome measures). These findings confirmed that *Z. jujube*, and frankincense supplementation effectively reduce pain and improve functional outcomes in OA patients, supporting their use as a complementary treatment alongside standard therapies.

Keywords: Frankincense; osteoarthritis; knee; *Zizyphus jujube*

Introduction

Osteoarthritis (OA) occurs as the most frequent kind of joint disease in humans, mainly affecting the knee, hip, and spine [1] As the leading cause

of disability and reliance, it is related to the aging process [2]. There is presently no definite treatment for the pain associated with OA. Moreover, conventional symptomatic alleviation

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procedures are prohibitively expensive in the current economic state [3]. There are many remedies for the symptomatic treatment of OA, including non-prescription and prescription analgesics. Only a handful of them have undergone rigorous testing in studies with proper placebo-controlled designs. In contrast, numerous medications utilized in OA are painkillers and other related substances that exhibit a high incidence of side effects [4]. These medications tend to offer relief from symptoms but do not cure the underlying condition. OA can also lead to complications over an extended period due to its chronic nature, requiring medication to be taken for an extended duration [5]. In contrast, it is essential to have methods and techniques in place to prevent the manifestation of symptoms. In this context, compounds from plants can be effective. These compounds typically lead to fewer side effects in the long term at low doses when compared to non-steroidal painkillers or corticosteroids. In addition, these compounds may play a more appropriate preventive role [5]. Therefore, it is necessary to conduct further studies on these plants and their derived compounds. In this regard, using mixtures of plant-derived compounds may act as a good choice for prevention and palliative treatment of OA.

Herbal medicines have been traditionally used for pain relief in OA, but there has been a recent revival of interest in these medications [6]. They have been examined in clinical studies as supplemental therapy alongside normal drugs because they do not have significant adverse effects. They are even sold as over-the-counter medications in pharmacies in circumstances when their efficacy has been shown [6]. Two of the herbal medicines been proven to have antioxidant, analgesic, and anti-inflammatory effects in tests are jujube and frankincense [7]. *Ziziphus jujuba*, often known as jujube or Chinese date, is a tiny tree [8]. The fruit may be eaten, and the dried fruit and seeds are utilized in Chinese traditional medicine [9]. The extract is used to treat anxiety and sleeplessness, although it has a recognized adverse effect of diarrhea [10]. The fruit, which resembles a little date, includes betulinic acid, oleanolic acid, maslinic acid, glucose, sitosterol,

stigmasterol, desmosterol, resin, catechol, tannin, essential oil, 13 different types of amino acids, selenium, calcium, phosphorus, and iron [11-13]. No research with healthy volunteers has been undertaken since it is classed as a food ingredient. Olibanum, popularly known as "Frankincense," is a hardened gum-like substance derived from the *Boswellia* tree's trunk [14]. Its oil is used on the skin and in aromatherapy [15]. Some bacteria and fungi appear to be killed by frankincense [14]. It's a popular scent in soaps, lotions, and fragrances [16]. The purpose of the present study was to investigate the efficacy of *Z. jujuba*/frankincense as a therapy for osteoarthritis pain in a placebo-controlled trial.

Materials and Methods

The study was a randomized controlled clinical trial with convenient sampling through random allocation in patients referred to the rheumatology clinic of Rasoul Akram Hospital. Inclusion criteria included age 50 to 70 years, chronic knee pain for at least 4 months before and diagnosis of knee arthritis by a rheumatologist, CRP less than 10, ESR less than 20, absence of liver, kidney and heart disorders, no use of glucocorticoid in the last three months, no intra-articular injection of hyaluronic acid in the last 6 months, no inflammatory joint diseases such as rheumatoid arthritis, poly-articular gout, no gastric and duodenal ulcers, no arthroscopic procedure in the last three months, the absence of pregnancy and breastfeeding. Complete non-use of the medicine (less than 80% of the drug) or non-use for more than three consecutive days, as well as refusal to complying in the trial, were criteria for withdrawal from the study.

The sample size was obtained using the technique for estimating sample size by comparing two proportions of 30 participants in each group, taking into account the type-one error of 5%, the accuracy of 95%, and assuming a 30% reduction in pain [17]. However, due to participant dropout, the final numbers were 21 in the test group and 25 in the control group. The impact of this discrepancy was addressed through statistical adjustments, ensuring that findings remained valid despite the reduced sample size. The subjects were assigned into two treatment and

control groups in this study using a block random allocation approach with four recruitment blocks. After gaining the patient's written consent, the test group participants were treated for one month with regular physician-ordered medications, including unsaponifiable Avocado-Soybean, Glucosamine as well as therapy with jujube/frankincense pills at a daily dose of two pills, one in the morning and one at night. Jujube/frankincense pill with anti-nociceptive and anti-inflammatory effects contained 250 mg of jujube active substance, 100 mg of frankincense active ingredient, and 25 mg of aloe vera. Medication adherence was monitored by collecting, and inspecting returned pills at each follow-up visit. Participants who took less than 80% of their prescribed medication or missed more than three consecutive days of treatment were excluded from the final analysis.

For the control group, patients were given the same standard physician-prescribed medications, for one month. Demographic information, patient background characteristics, and treatment

outcomes were gathered using two tools: The Western Ontario and McMaster Universities Osteoarthritis Index, WOMAC questionnaire (with three sections of questions relating to pain, dryness, and function) and the Visual Analog Scale, VAS questionnaire for pain measuring criteria. Information from the WOMAC questionnaire was obtained in two stages: before the commencement of therapy and one month afterward. VAS questionnaire data was obtained in three phases before the commencement of therapy, as well as one week and one month thereafter. In order to follow up with patients, cell phone numbers were obtained and the necessary follow-ups were done by one of the researchers.

The data gathered by the questionnaire was firstly classified based on the WOMAC variables and areas. Then it was entered into the SPSS18 software, and the data analysis was done using the t-test, repeated measure, univariate analysis method, which was based on the normal distribution of the data. When necessary, descriptive statistics and chi square were applied.

Table 1. Demographic characteristics of the samples in the two studied groups

Parameter	Study Group	Control Group	P value
Number of participants	21	25	
Male/Female	3/18	1/24	0.300
Education level			0.900
<Diploma	8	9	
Diploma	7	9	
Graduated from Universities	6	7	
Average income	500 \$	500 \$	

Ethical Consideration

All patients were fully informed about the intervention and its potential outcomes, as written agreement to participate in the trial was acquired. Patients might opt out of the research at any point throughout treatment. Patients were given a cell phone number where they may ask inquiries at any time. The follow-ups were carried out in the same manner. All patients-related information was considered confidential and remained with the research team. The information that leads to the disclosure of the identity of individuals will not be published. The project's ethical code is IR.SBMU.RETECH.REC.1400.475. This project

was also registered as a clinical trial in IRCT by registration number IRCT20150411021697N2.

Results

The treatment and control groups each had 25 participants. One member of the treatment group refused to participate in the questioning. Three participants in the treatment group developed diarrhea and stopped taking the medication, so they were removed from the research. Finally, 21 participants were retained in the treatment group and 25 participated in the control. No significant adverse effects were reported in the control group,

but any mild to moderate adverse events were monitored and recorded for both groups throughout the study. The treatment group's average age was 56.6 years with a standard deviation of 8.79 years, whereas the control group's average age was 59.5 years with a standard deviation of 9.62 years ($P=0.29$).

Demographic details are noted in [Table 1](#). They were similar in both groups of intervention. There was no statistically significant difference in sex distribution between the two intervention groups. The research medicine was taken by all of the patients, as evidenced by the used vials returned at each appointment.

Table 2. Tests of Within-Subjects Contrasts

Source	Time	Type III Sum of Squares	df	Mean Square	F	p
Time	Linear	96.764	1	96.764	63.415	0.000
	Quadratic	0.033	1	0.033	0.080	0.779
Time*group	Linear	19.927	1	19.927	13.059	0.001
	Quadratic	0.002	1	0.002	0.004	0.949
Error (Time)	Linear	62.561	41	1.526		
	Quadratic	16.797	41	0.410		

To analyze dryness and mobility limitation, univariate analysis was employed. It was shown that there was a statistically significant difference between the groups, before and after the WOMAC test ($F = 63.4$, $P=0.001$) ([Table 2](#)). These results showed that the treated and the control groups had significant differences in response to the pain test. The intensity of the pain parameter in people who used

Jujube/Frankincense mixture as a supportive therapy to alleviate the pain with knee osteoarthritis was significantly different from people who did not use this mixture. This significant difference was also clearly observed at different time intervals after the start of treatment ($p = 0.001 < 0.05$). The status of WOMAC scores in the two groups has been summarized in [Figure 1](#).

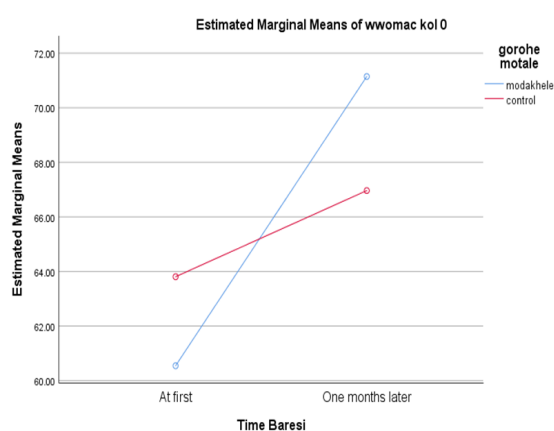


Figure 1. The status of WOMAC scores in two groups

In [Table 3](#), between-group ANOVA analysis shows that the WOMAC scores in pain, stiffness, and function were statistically different between

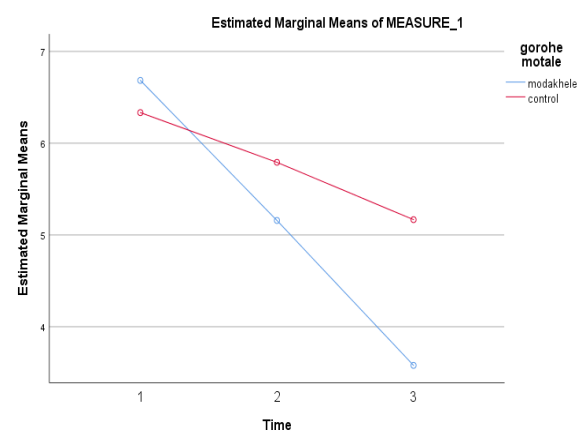


Figure 2. The status of VAS scores in two groups

the groups in different follow-ups. Within-group analysis in each group revealed the total WOMAC score was different between before,

after one-week, and one-month of intervention. Comparing means revealed that before intervention WOMAC was different from both

one-week, and one-month follow-ups; but there was no difference between one-week and one-month follow-ups.

Table 3. WOMAC score before, one week, and one month after intervention in study groups

Time	WOMAC pain score (0-20)	WOMAC stiffness score (0-8)	WOMAC physical function (0-68)
Before	14.56 ± 3.24	6.74 ± 1.17	48.03 ± 12.17
One week later	13.90 ± 3.50	6.24 ± 1.19	47.00 ± 13.99
One month later	13.33 ± 4.09	6.22 ± 1.48	43.40 ± 12.91
Cohen's d (Before vs one month)	0.330		
P-value (Before vs one month)	0.147		

The average VAS scores are disclosed in [Table 4](#). The scores were recorded initially, a week, and one month after the commencement of therapy in two groups to assess pain severity using the Repeated Measure test. Between-groups analysis of ANOVA proved that the intervention reduced

the pain compared to the baseline in the follow-ups. There was statistical difference between test and control groups based on the Kellgren-Lawrence classification of osteoarthritis. Within-group analysis has been done by comparing means among three measurements of the groups

Table 4. Study Group*Time

Study Group	Time	Mean	Std. Error	95% Confidence Interval	
				Lower	Upper
Test	1	6.684	0.441	5.794	7.575
	2	5.158	0.484	4.180	6.135
	3	3.579	0.541	2.486	4.671
control	1	6.333	0.392	5.541	7.126
	2	5.792	0.431	4.922	6.661
	3	5.167	0.481	4.195	6.139

using a post-hoc test. There was a statistically-significant difference in the VAS score between the groups when compared at different periods ([Table 5](#)). [Figure 2](#) summarizes the status of VAS scores in two groups. It showed that before interv-

ention VAS score was different from one-week, and one-month follow-up; but there was no significant difference. The difference between measures taken at different times was significant in the repeated measure test ($F = 321.4$, $P = 0.001$).

Table 5. Pairwise Comparisons

(I) Time	(J) Time	Mean Difference (I-J)	Std. Error	Sig. ^b	95% CI for difference ^b	
					Lower Bound	Upper Bound
1	2	1.034*	0.164	0.000	0.625	1.443
	3	2.136*	0.268	0.000	1.466	2.806
2	1	-1.034*	0.164	0.000	-1.443	-0.625
	3	1.102*	0.195	0.000	0.615	1.589
3	1	-2.136*	0.268	0.000	-2.806	-1.466
	2	-1.102*	0.195	0.000	-1.589	-0.615
Cohen's d (VAS: Before vs one month)		0.33				
P-value (VAS: Before vs one month)		0.147				

Discussion

The results of this analysis revealed that prescribing jujube and frankincense pills as a supplement had a substantial effect on discomfort, joint dryness, and limitation of movement. In this trial, jujube and frankincense pills improved the pain severity of OA. The findings of a previous research has demonstrated the potential benefits of frankincense in alleviating knee pain [18], and our findings are consistent with these reports. However, there is limited literature on the combined effects of jujube and frankincense for OA management. This study's strength lies in its novel approach - utilizing a complementary herbal extract to reduce pain without the adverse effects commonly associated with conventional pharmaceuticals. Given the absence of significant differences in demographic characteristics such as age, gender, and education between the treatment and control groups, the observed effects are unlikely to be influenced by confounding variables. This suggests that the intervention had a genuine therapeutic impact. Despite its promising findings, this study has several limitations: The sample size was small, and the duration of intervention lasted only one month therefore future studies with larger sample size and longer duration is needed the confirm the results and ensure broader applicability. The possible biases of this study where are that participants were recruited from a single rheumatology clinic, which may not represent the general population of OA patients and the placebo effect. While a control group was included, a placebo arm was not utilized. This means that improvements in the intervention group may have been influenced by psychological factors rather than the treatment itself.

Conclusion

Oral administration of *Z. jujuba*/frankincense resulted in considerable reductions in pain intensity linked with knee arthritis. This may be a sign of *Z. jujuba*'s increasing influence over processes involved in pain sensation; analgesic capabilities have been established in numerous plant species and plant products used in medicine. They likewise have no detrimental effects on health. This was simply a preliminary investigat-

tion to verify *Z. jujuba*/anti-nociceptive frankincense's efficacy. With the verified results, additional research may lead to a decline in the dosage of nonsteroidal anti-inflammatory medicines (NSAIDs) in osteoarthritis, as well as a drop in drug adverse effects. Nevertheless, further research should focus on determining the active ingredients of *Z. jujuba*/frankincense as well as the mechanism of *Z. jujuba*/frankincense.

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Conflict of Interest

All authors certify that they have NO affiliations with or involvement in any organization or entity with any financial or non-financial interest in the subject matter or materials discussed in this manuscript.

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References

1. Katz JN, Arant KR, Loeser RF. Diagnosis and Treatment of Hip and Knee Osteoarthritis: A Review. *Jama* 2021; 325(6):568-78. doi: 10.1001/jama.2020.22171.
2. Allen KD, Thoma LM, Golightly YM. Epidemiology of osteoarthritis. *Osteoarthritis Cartilage* 2022; 30(2):184-95. doi: 10.1016/j.joca.2021.04.020.
3. Yahaya I, Wright T, Babatunde OO, Corp N, Helliwell T, Dikomitil L, Mallen CD. Prevalence of osteoarthritis in lower middle- and low-income countries: a systematic review and meta-analysis. *Rheumatol Int* 2021; 41(7):1221-31. doi: 10.1007/s00296-
4. O'Neil CK, Hanlon JT, Marcum ZA. Adverse effects of analgesics ommonly used by older adults with osteoarthritis: focus on non-opioid and opioid analgesics. *Am J Geriatr*

- Pharmacother* 2012; 10(6):331-42. doi: 10.1016/j.amjopharm.2012.09.004.
5. Gregori D, Giacobelli G, Minto C, Barbetta B, Gualtieri F, Azzolina D, et al. Association of pharmacological treatments with long-term pain control in patients with knee osteoarthritis: A systematic review and meta-analysis. *Jama* 2018; 320(24):2564-79. doi: 10.1001/jama.2018.19319.
 6. Cutolo M, Berenbaum F, Hochberg M, Punzi L, Reginster JY. Commentary on recent therapeutic guidelines for osteoarthritis. *Semin Arthritis Rheum* 2015; 44(6):611-7. doi: 10.1016/j.semarthrit.2014.12.003.
 7. Niazi A, Rahimi VB, Askari N, Rahmanian-Devin P, Askari VR. Topical treatment for the prevention and relief of nipple fissure and pain in breastfeeding women: A systematic review. *Advances in Integrative Medicine* 2021; 8(4):312-21.
 8. Shahrajabian MH, Sun W, Cheng Q. Chinese jujube (*Ziziphus jujuba* Mill.)—a promising fruit from Traditional Chinese Medicine. *Annales Universitatis Paedagogicae Cracoviensis Studia Naturae* 2020:194-219. Rodríguez Villanueva J, Rodríguez Villanueva L. Experimental and Clinical Pharmacology of *Ziziphus jujuba* Mills. *Phytother Res* 2017; 31(3):347-65. doi: 10.1002/ptr.5759.
 9. Rodríguez Villanueva J, Rodríguez Villanueva L. Experimental and clinical pharmacology of *Ziziphus jujuba* Mills. *Phytotherapy Research* 2017; 31(3):347-65
 10. Sobhani Z, Nikoofal-Sahlabadi S, Amiri MS, Ramezani M, Emami SA, Sahebkar A. Therapeutic effects of *Ziziphus jujuba* Mill. fruit in traditional and modern medicine: a review. *Med Chem* 2020; 16(8):1069-88. doi: 10.2174/1573406415666191031143553.
 11. Chen J, Liu X, Li Z, Qi A, Yao P, Zhou Z. et al. A review of dietary *Ziziphus jujuba* fruit (Jujube): Developing health food supplements for brain protection. *Evid Based Complement Alternat Med* 2017; 2017. doi: 10.1155/2017/3019568.
 12. Chen J, Tsim KW. A Review of edible jujube, the *Ziziphus jujuba* fruit: A health food supplement for anemia prevalence. *Frontiers in Pharmacology* 2020; 11:593655.
 13. Mahajan R, Chopda M. Phyto-Pharmacology of *Ziziphus jujuba* Mill-A plant review. *Pharmacognosy Reviews* 2009; 3(6):320.
 14. Almeida-da-Silva CLC, Sivakumar N, Asadi H, Chang-Chien A, Qoronfleh MW, Ojcius DM, Essa MM. Effects of Frankincense compounds on infection, inflammation, and oral health. *Molecules* 2022; 27(13):4174. doi: 10.3390/molecules27134174.
 15. Bonilla IV, Garcia D, Abbott A, Spruill L, Siegel J, Forcucci J, et al. The anti-proliferative effects of a Frankincense Extract in a window of opportunity phase Ia clinical trial for patients with breast cancer. 2022.
 16. Almeida-da-Silva C, Sivakumar N, Asadi H. Effects of Frankincense Compounds. In: Scholarly Community Encyclopedia. 2022
 17. Khoramjouy M, Bayanati M, Noori S, Faizi M, Zarghi A. Effects of *Ziziphus Jujuba* Extract Alone and Combined with *Boswellia Serrata* Extract on Monosodium Iodoacetate Model of Osteoarthritis in Mice. *Iran J Pharm Res* 2022; 21(1):e134338. doi: 10.5812/ijpr-134338.
 18. Al-Yasiry ARM, Kiczorowska B. Frankincense therapeutic properties. *Postepy Hig Med Dosw (Online)* 2016; 70:380-91. doi: 10.5604/17322693.1200553.