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Effect of *Delphinium denudatum* Wall. (Jadwar) on knee osteoarthritis: A randomized double-blinded placebo-controlled clinical trial

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Trial registration number: IRCT20181218042037N1 at Iranian Registry of Clinical Trials (IRCT) (https://en.irct.ir/trial/38632)

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Abstract

Introduction: Osteoarthritis (OA) is the most common disease of joints. The management of OA is challenging due to the efficacy and safety of treatments. In recent decades, traditional herbal medicines have been introduced for treatment of disease. Delphinium denudatum Wall. (Jadwar) is a medicinal herb with a long-lasting usage in traditional Persian medicine for joint diseases. The present study aimed to investigate the effect of Jadwar on pain and symptoms of knee OA.

Methods: In this randomized double-blind placebo-controlled trial, 104 patients with knee OA were randomly assigned into two groups of intervention and control. While the intervention group received one Jadwar capsule (500 mg) twice a day for four weeks, the control group received placebo capsules. The primary outcomes, including pain, stiffness, and physical activity were evaluated using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) questionnaire and the Visual Analogue Scale (VAS) at baseline two and four weeks after the intervention.

Results: Ninety-four participants completed the study. Considering the time of interaction, after four weeks, data analysis revealed a significant decrease in the VAS score (37.23±12.58 vs. 57.87±13.21), total WOMAC score (24.83±9.70 vs. 49.17±12.89), WOMAC pain score (7.19±2.90 vs. 12.40±4.46), stiffness (2.06±0.845 vs. 4.11±1.14), and physical function (15.57±7.25 vs. 32.66±9.78) in the intervention group compared to the control group (P<0.0001 for all outcomes). Additionally, no serious adverse effects were reported.

Conclusions: Jadwar can be suggested as a safe medicinal plant for knee OA because it can relieve the pain and symptoms of OA.
Keywords: Delphinium denudatum Wall, Herbal medicine, Jadwar, Knee osteoarthritis, Traditional Persian medicine

1. Introduction

Osteoarthritis (OA) is a chronic disease of synovial joints characterized by slow progressive loss of the articular cartilage, along with deterioration of ligaments and joint capsule hypertrophy. It is the prior cause of pain and disability in the elderly.\textsuperscript{1,2} OA is highly prevalent in the United States and other countries.\textsuperscript{3} Current treatment options are physical exercise, nonsteroidal anti-inflammatory drugs (NSAIDS), corticosteroid injections, intra-articular hyaluronic acid (HA), and joint replacement surgery.\textsuperscript{4,5} The conventional treatment aims to slow the pace of the cartilage degradation process and to alleviate pain and inflammation. However, there are different adverse events related to these treatments.\textsuperscript{6-8}

Studies have shown the growing trend of using complementary and alternative medicine, including herbal medicine usage in the management of various diseases.\textsuperscript{9,10} Traditional Persian Medicine (TPM), as one of the oldest complete medical systems, provides various products, therapies, and health care recommendations.\textsuperscript{11,12} So far, only one clinical trial has been conducted on the effects of Jadwar, reporting no side effects.\textsuperscript{13}

*Delphinium denudatum* Wall. (Ranunculaceae) is one of the most important folk medicinal plants in the indigenous systems of medicine in India, Pakistan, and Iran. It is also known as Jadwar, which is used to treat different diseases. In TPM, Jadwar is used for its therapeutic effects such as antiepileptic, antiseptic, anti-inflammatory, cardiotonic, and analgesic ones. In addition, it has been recommended for managing opium addiction, snakebites, arthritis, and joints pain.\textsuperscript{13-15}
The mechanisms behind the pharmacological action of *Delphinium denudatum* Wall. can significantly be assisted by the isolation of its active principle from the roots and determination of its structural and functional relationship. The chemical and phytochemical analysis of the Jadwar's roots has identified various active components, including different alkaloids (such as delphinine, stahisagrine, delphocurarine, condelphine, denudatin, and isotalatizidine), sterols, fatty acids, sugar, protein, starch, and flavonoids. Furthermore, phenolic groups and tannins, carbohydrate, steroids, amino acids, glycosides, and terpenoids are present in the extracts of *Delphinium denudatum* Wall. Quercetin is the main flavonoid content of Jadwar with antioxidant, anti-inflammatory, anti-aging, neuroprotective, anti-fatigue, and cardioprotective properties. According to some previous studies, the aqueous and alcoholic extracts of Jadwar roots have antinociceptive and anti-inflammatory properties. It is also known as a rich source of diterpenoid and norditerpenoid alkaloids with analgesic activities. The antinociceptive effects of diterpenoid alkaloids are due to deceleration of nerve conductivity at various stages of passing through pathways of pain sensation. In addition, several animal studies demonstrated the antinociceptive effects of the aqueous root extract of Jadwar on the thermal and chemical models of analgesia. Accordingly, this study aimed to evaluate the effect of Jadwar on pain and symptoms of knee OA.

2. Methods

2.1. Study design

This study was designed as a randomized, double-blinded, placebo-controlled superiority clinical trial. The participants were randomly allocated into two arm parallel groups (drug and placebo) (1:1 allocation ratio) using similar capsules. Both participants and researchers were unaware of the group allocations until the end of the study. The study protocol was registered in the Iranian...
Registry of Clinical Trials (IRCT20181218042037N1). Also, the study was approved by the Ethics Committee of Tabriz University of Medical Science (code: IR.TBZMED.REC.1397.1054).

**2.2. Participants**

Following the CONSORT guidelines, written informed consent was obtained from each patient before participation in the study. The inclusion criteria were being in the age range of 40–70 years, signing an informed consent, having mild to moderate knee OA based on the Kellegren-Lawrence (KL) grading scale and existence of knee joint pain for at least three months without having any congenital abnormality of lower extremities. Diagnosis of knee OA was made by a physician as stated by the American College of Rheumatology (ACR) criteria.\(^{23,24}\) The exclusion criteria were as follows: having secondary OA (such as rheumatoid arthritis, traumatic arthritis, and gout), history of joint replacement surgery, history of corticosteroid injection in the past three months, using oral or topical corticosteroids in the past 14 days, using analgesic drugs three days prior to participation, pregnancy or breastfeeding, history of allergic reaction to Jadwar, drug abuse, history of any acute or chronic disease (such as diabetes and/or hypertension), any skin lesions or trauma on the affected knee, using other therapeutic modalities (such as physiotherapy and/or acupuncture) in the past two weeks, and body mass index (BMI) $\geq 35$ kg/m$^2$.

This study was conducted in Shohada Hospital of Tabriz, Iran from June to December 2019.

**2.3. Randomization, blinding, and concealment of allocation**

The OA patients were divided into drug (Jadwar) and placebo groups using block design randomization (block size of 2:4). Randomization was carried out using a computer-generated list by the Rand List (version: 1.2) software with 1:1 allocation ratio. The sealed envelopes were used for allocation concealment. The same capsules with identical color and shape and odor were used
in both groups. The patients and researchers were blind to the allocations. Random allocation sequence was conducted by an independent investigator with no clinical involvement in the trial.

2.4. Intervention

While the treatment group received Jadwar capsules, the control group received placebo capsules in two divided doses for each group (one capsule per dose) every day for four weeks. The Jadwar capsule (Habb-e-Jadwar) is a product industrialized by Shefanegar Nazari Pharmaceutical Company, Qom, Iran. Each Jadwar capsule (Iran FDA permission No. T-S-93-0204) contained 500 mg of *D. denudatum* root powder. Previous studies achieved its herbarium verification and microbiological evaluations measuring the total flavonoid and total phenol content; they also provided High Performance Liquid Chromatography (HPLC) fingerprints of the drug sample in three different wavelengths. Furthermore, the placebo capsules contained 500 mg of the starch powder in the same container regarding the shape and color. The participants were followed during the study regarding the accurate use of the capsules. The researchers called the patients every three days and visited them on days 7, 14, and 21 to assess their adherence and possible side effects. They were also asked about any adverse effects according to the side effect questionnaire (Appendix 1). The patients used acetaminophen tablets (up to 1 g/day) to relieve pain if needed. It was impossible to determine the cut-off point for intolerance because the pain intolerance was individual and sex-dependent.

2.5. Outcomes

The primary outcomes included knee pain, knee stiffness, and the physical function of patients. The knee pain was evaluated using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and the Visual Analogue Scale (VAS). Meanwhile, the knee stiffness and physical function of patients were evaluated by WOMAC. All the outcomes were evaluated at
baseline two and four weeks after the intervention. The VAS score ranged from zero (no pain) to 100 (maximum of pain). Additionally, the Persian version of the WOMAC questionnaire was used to assess the disease at the starting point, as well as two and four weeks after the intervention. This questionnaire evaluates the patients in three dimensions (subscales) of pain, physical function, and stiffness. The reliability and validity of the questionnaire were approved in a previous study.25

The secondary outcome was the amount of acetaminophen intake, which was measured by the daily intake of the acetaminophen (mg/day).

2.6. Sample size

The sample size was calculated to compare the mean changes in the severity of pain based on the VAS scale (0-100). To detect the minimum clinically significant change of ±15 points on the pain scale (based on a pilot study on five individuals), assuming a standard deviation of 20, power of 0.95%, and Type I error equal to 0.05 for two groups, the sample size was calculated as 94 patients. Considering the 10% loss to follow-up, the final sample size in each group was calculated as 52.

2.7. Statistical analysis

Statistical analysis was conducted using the SPSS PC Statistics Software, version 18.0. The Kolmogorov-Smirnov test was applied to demonstrate the distribution of the quantitative data. The independent samples t-test and the Mann-Whitney U test were used to compare the differences between the two independent groups. In this study, the comparison of the means before and after prescription of drug and placebo was made using the paired samples t-test and the Wilcoxon's test. The variables were separately evaluated in each group by the repeated measures analysis of variance (ANOVA) in three measurement times. The results were presented as mean ± standard deviation. Both per-protocol analysis and intention-to-treat analysis were used regardless of the
treatment received by the patients. Furthermore, $P$-value <0.05 was considered as statistically significant.

3. Results

3.1. Study flow

Out of a total of 131 patients, 104 patients were eligible to be included in the study. These patients were randomly assigned into two groups of intervention and control. All patients were analyzed for the primary outcome and 94 individuals completed the study. Figure 1 presents the detailed flow of the study. The mean age of participants was 57.33 ± 8.85 and 59.43± 7.82 years in Jadwar and placebo groups, respectively. Also, 57 (54.8%) patients were female and 47 (45.2%) were male. The patients’ demographic data and baseline clinical characteristics were not different between the groups; except for WOMAC pain score and total WOMAC score (Table 1). To avoid the effects of heterogeneous baseline values of these two variables on the main results, the effects of baseline values were considered and controlled as the disturbing variables in the repeated measures ANOVA.

3.2. Study outcomes

The results showed a significant improvement ($P<0.001$) in all the outcomes over the study time, including VAS, total WOMAC, WOMAC pain score, stiffness, and physical function in both groups. Table 2 depicts the mean differences of the two time spots, within-group changes in each group, and exact $P$-values for these comparisons. Comparison of the outcome measures regarding the mean values at each time spot showed significant difference between groups at baseline for WOMAC pain score and total WOMAC ($P=0.001$ and $P=0.019$, respectively). After two weeks, there was a significant difference for VAS and physical function between the two groups ($P=0.011$
and $P = 0.021$, respectively). After four weeks, there was a significant difference between the two groups for all outcomes ($P < 0.001$). Table 3 presents the inter-group analysis for different measurement times. According to the results, 42 patients in Jadwar group and two patients in placebo group showed at least 15 points improvement in VAS score. Jadwar capsule was well-tolerated by the patients, and no adverse effects were identified in the follow-up assessments. The use of acetaminophen was significantly lower in the Jadwar group than in the placebo group; however, there was no significant difference between the two groups at the first 14 days of the study (Table 4).

4. Discussion

The aim of this study was to investigate the effect of Jadwar on pain and symptoms of knee OA. The results demonstrated the effectiveness of Jadwar in improving OA symptoms, as represented by improvement in all outcome measures, including VAS and WOMAC scores. The study outcomes were measured at two cut-off time intervals (two and four weeks after the intervention). The VAS score and physical function had a significant improvement in the intervention group (Jadwar) compared to the placebo group at the two cut-off time intervals. The reductions in the stiffness, WOMAC pain score, and total WOMAC score were significant in the intervention group compared to the placebo group only four weeks after the intervention. This improvement was not statistically significant two weeks after the intervention, despite the improvement of the outcomes. This issue can be explained in two ways. The lack of a significant difference at the end of the second week of treatment may be due to the small sample size and its effect on statistical analysis. Also, it is possible that Jadwar shows its effect over time and better results are obtained over the time. But the VAS score two weeks after the intervention was statistically significant. This difference in results between the two questionnaires may be due to the fact that the VAS is a
subjective questionnaire, and the patient directly determines the amount of pain on the questionnaire, but the WOMAC questionnaire is an objective questionnaire usually filled by another person. Also, the VAS questionnaire is a simple questionnaire, but the WOMAC questionnaire has several complex items. The consumption of acetaminophen at weeks three and four was significantly lower in Jadwar group compared to the placebo group; this may represent the effects of Jadwar in reducing pain of knee OA.

Previous clinical investigations confirmed the effectiveness of some herbal medicines in the treatment of knee OA. For instance, in some previous studies, consuming ginger (250 mg capsules, twice daily for six weeks)\textsuperscript{26} and curcuminoids (1500 mg/day; bioactive components of turmeric) for six weeks\textsuperscript{27} decreased the pain and ameliorated the physical function of patients with knee OA according to VAS and WOMAC scores. In addition to oral dosage forms, a clinical study revealed that the topical use of Dwarf Elder (\textit{Sambucus ebulus} L.) gel in three divided doses every day for four weeks improved the knee-joint pain, stiffness, and physical function in patients with knee OA.\textsuperscript{28} Topical use of the sesame (\textit{Sesamum indicum} L.) oil in these patients was also non-inferior to the diclofenac gel in terms of pain reduction and physical function based on VAS and WOMAC scores.\textsuperscript{29} Moreover, the use of a topical formulation of chamomile oil decreased the analgesic demand of knee OA patients in another clinical trial.\textsuperscript{30} Furthermore, other studies demonstrated the non-pharmacological treatments of knee OA, such as leech therapy.\textsuperscript{31-33}

Not only clinical studies but also animal experimentations have revealed the analgesic effects of \textit{Delphinium denudatum} Wall. A dose-related analgesic effect of the \textit{Delphinium denudatum} Wall. root aqueous extract at four dose levels (200-1600 mg/kg) was confirmed in thermal and chemical models of the analgesia.\textsuperscript{22} Moreover, the ethanolic extract of \textit{Delphinium denudatum} Wall. in low (300 mg/kg) and high (600 mg/kg) doses, as well as the methanol fraction in low (200 mg/kg) and
high (400 mg/kg) doses exhibited a statistically significant increase in the reaction time and pain threshold in both Eddy’s hot plate and Tail flick tests in Wistar albino rats. Indeed, the degree of analgesia correlates positively with the doses of *Delphinium denudatum* Wall. extracts. Jadwar is known as a rich source of diterpenoid and norditerpenoid alkaloids. Diterpenoid alkaloids selectively interact with nicotinic acetylcholine receptors in the central nervous system and possess significant analgesic activity. The ethanolic extract of *Delphinium denudatum* Wall. contains the free radical $\alpha$-diphenyl-$\beta$-picrylhydrazyl (DPPH) and superoxide-scavenging inhibitors acting as primary antioxidants, whereas ethyl acetate had hydroxyl radical scavenger as primary antioxidants. The $\beta$-sitosterol from the roots of Jadwar is one of the phytosterols with a chemical structure identical to that of cholesterol and has the ability to scavenge the radicals generated by DPPH method. This suggests that $\beta$-sitosterol has potential antioxidant properties. Furthermore, other reports have shown the significant free radical scavenging capacity of $\beta$-sitosterol.

OA is a disease with the involvement of inflammatory mediators released by bone, cartilage, and synovium. Recent studies have proven that OA progression is significantly associated with the oxidative stress. Therefore, targeting the oxidative stress signaling pathways and the inflammation process should be considered in investigating the potential therapeutic approaches of OA.

In this regard, quercetin has shown antioxidant and anti-inflammatory properties as one of the most important flavonoid contents of Jadwar. It may play a crucial role in the functional and symptomatic improvement of patients suffering from knee OA. Moreover, $\beta$-Sitosterol in Jadwar rhizome is one of the phytosterols, which can scavenge the free radicals generated by $\alpha$-diphenyl-$\beta$-picrylhydrazyl (DPPH) and has potential antioxidant properties. In fact, various active
ingredients of Jadwar have revealed their antioxidant, anti-inflammatory, and analgesic properties and can explain the potential of Jadwar for the treatment of OA.\(^{39}\)

This is the first clinical trial to evaluate the effect of Jadwar on knee OA. According to our results, this herbal medicine can be used as an analgesic. Also, the four-week consumption of Jadwar capsules considerably improved the perception of patients regarding their pain, stiffness, and physical function. However, further studies should be conducted to confirm its effects in different populations.

5. Limitations

One of the important limitations of this trial was its short follow-up time. Absence of objective outcome measures to evaluate the functional status was another limitation of the study.

6. Conclusion

Jadwar could be suggested as an effective natural medicine for patients with mild-to-moderate knee OA. These promising results can motivate other researchers to conduct further studies investigating its effectiveness in larger populations and even in other joint pains.

7. Declarations

**Ethics approval and consent to participate:** This study was approved by the Ethics Committee of Tabriz University of Medical Science, Iran (code: IR.TBZMED.REC.1397.1054).

**Consent for publication:** Not applicable.

**Availability of data and materials:** The datasets generated and/or analyzed during the current study are not publicly available due university policies but are available from the corresponding author on reasonable request.
Conflict of interests: The authors declare that they have no conflict of interests.

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Authors' contributions: RBN, ABK, and SD contributed to writing the main draft. RM and MB contributed to writing the introduction section. MG and RC regulated methods and performed analysis. SMF and MK supervised writing of the manuscript. All authors read and approved the final manuscript.

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References


Figure 1. Study flow diagram
Table 1. The baselines and demographic characteristics of the patients

<table>
<thead>
<tr>
<th></th>
<th>Jadwar group (n=52)</th>
<th>Placebo group (n=52)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Mean ±SD)</td>
<td>57.33 ± 8.85</td>
<td>59.43 ± 7.88</td>
<td>0.206</td>
</tr>
<tr>
<td>Gender n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>23 (44.2%)</td>
<td>24 (46.2%)</td>
<td>0.844</td>
</tr>
<tr>
<td>Female</td>
<td>29 (55.8%)</td>
<td>28 (53.8%)</td>
<td></td>
</tr>
<tr>
<td>BMI (Mean ±SD)</td>
<td>26.17±2.90</td>
<td>25.25±3.45</td>
<td>0.143</td>
</tr>
<tr>
<td>VAS</td>
<td>64.26±14.33</td>
<td>62.87±13.17</td>
<td>0.627</td>
</tr>
<tr>
<td>Stiffness</td>
<td>4.60±1.31</td>
<td>4.49±1.33</td>
<td>0.698</td>
</tr>
<tr>
<td>Physical function</td>
<td>40.74±9.90</td>
<td>37.53±9.67</td>
<td>0.115</td>
</tr>
<tr>
<td>WOMAC Pain Score</td>
<td>18.00±4.15</td>
<td>14.83±4.72</td>
<td>0.001</td>
</tr>
<tr>
<td>Total WOMAC</td>
<td>63.34±12.85</td>
<td>56.85±13.41</td>
<td>0.019</td>
</tr>
</tbody>
</table>

SD: Standard Deviation; BMI: Body Mass Index; VAS: visual analogue scale; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index
Table 2. Changes of outcome measures (mean ± SD) before and after the intervention.

<table>
<thead>
<tr>
<th>Measure</th>
<th>Baseline</th>
<th>After 2 weeks</th>
<th>Baseline</th>
<th>After 4 weeks</th>
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<tr>
<td></td>
<td>N</td>
<td>Mean ± SD of difference</td>
<td>P-value</td>
<td>Mean ± SD of difference</td>
</tr>
<tr>
<td>VAS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jadwar</td>
<td>52</td>
<td>13.085±6.039</td>
<td>&lt;0.001</td>
<td>27.021±10.356</td>
</tr>
<tr>
<td>Placebo</td>
<td>52</td>
<td>4.894±3.969</td>
<td>&lt;0.001</td>
<td>5.000±4.663</td>
</tr>
<tr>
<td>Stiffness</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jadwar</td>
<td>52</td>
<td>1.021±.766</td>
<td>&lt;0.001</td>
<td>2.532±1.442</td>
</tr>
<tr>
<td>Placebo</td>
<td>52</td>
<td>.851±.908</td>
<td>&lt;0.001</td>
<td>.383±.795</td>
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<tr>
<td>Physical function</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jadwar</td>
<td>52</td>
<td>13.191±7.790</td>
<td>&lt;0.001</td>
<td>25.170±10.532</td>
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<tr>
<td>Placebo</td>
<td>52</td>
<td>5.681±4.746</td>
<td>&lt;0.001</td>
<td>4.872±4.689</td>
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<tr>
<td>WOMAC Pain Score</td>
<td></td>
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<td></td>
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<tr>
<td>Jadwar</td>
<td>52</td>
<td>5.894±2.530</td>
<td>&lt;0.001</td>
<td>10.809±3.916</td>
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<tr>
<td>Placebo</td>
<td>52</td>
<td>2.489±2.283</td>
<td>&lt;0.001</td>
<td>2.426±1.975</td>
</tr>
<tr>
<td>Total WOMAC</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Jadwar</td>
<td>52</td>
<td>20.107±8.847</td>
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<td>38.511±12.576</td>
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<td>Placebo</td>
<td>52</td>
<td>9.021±7.216</td>
<td>&lt;0.001</td>
<td>7.681±6.276</td>
</tr>
</tbody>
</table>

SD: Standard Deviation; VAS: visual analogue scale; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index
Table 3. Comparison of mean difference of study variables between jadwar and placebo groups.

<table>
<thead>
<tr>
<th></th>
<th>Baseline (Mean±SD)</th>
<th>P value</th>
<th>After 2 weeks (Mean±SD)</th>
<th>P value</th>
<th>After 4 weeks (Mean±SD)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VAS</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Jadwar</td>
<td>64.26±14.33</td>
<td>0.627</td>
<td>51.17±12.60</td>
<td>0.011</td>
<td>37.23±12.58</td>
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<tr>
<td>Placebo</td>
<td>62.87±13.17</td>
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<td>57.98±12.83</td>
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<td>57.87±13.21</td>
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<tr>
<td><strong>Stiffness</strong></td>
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<td></td>
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</tr>
<tr>
<td>Jadwar</td>
<td>4.60±1.31</td>
<td>0.698</td>
<td>3.57±1.11</td>
<td>0.814</td>
<td>2.06±0.845</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Placebo</td>
<td>4.49±1.33</td>
<td></td>
<td>3.64±1.48</td>
<td></td>
<td>4.11±1.14</td>
<td></td>
</tr>
<tr>
<td><strong>Physical function</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Jadwar</td>
<td>40.74±9.90</td>
<td>0.115</td>
<td>27.55±8.63</td>
<td>0.021</td>
<td>15.57±7.25</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Placebo</td>
<td>37.53±9.67</td>
<td></td>
<td>31.85±9.07</td>
<td></td>
<td>32.66±9.78</td>
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<tr>
<td><strong>WOMAC Pain Score</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Jadwar</td>
<td>18.00±4.15</td>
<td>0.001</td>
<td>12.11±3.53</td>
<td>0.774</td>
<td>7.19±2.90</td>
<td>&lt;0.001</td>
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<tr>
<td>Placebo</td>
<td>14.83±4.72</td>
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<td>12.34±4.31</td>
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<td>12.40±4.46</td>
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<tr>
<td><strong>Total WOMAC</strong></td>
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<tr>
<td>Jadwar</td>
<td>63.34±12.85</td>
<td>0.019</td>
<td>43.23±12.09</td>
<td>0.079</td>
<td>24.83±9.70</td>
<td>&lt;0.001</td>
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<tr>
<td>Placebo</td>
<td>56.85±13.41</td>
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<td>47.83±13.00</td>
<td></td>
<td>49.17±12.89</td>
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</tbody>
</table>

SD: Standard Deviation; BMI: Body Mass Index; VAS: visual analogue scale; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index
Table 4. The mean (Q0.25, Q0.75) number of consumed acetaminophen tablets (500 mg) by each group

<table>
<thead>
<tr>
<th></th>
<th>Weeks 1-2</th>
<th>Weeks 3-4</th>
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</thead>
<tbody>
<tr>
<td>Jadwar</td>
<td>3.70 (0.00,7.00)</td>
<td>0.79 (0.00,0.00)</td>
</tr>
<tr>
<td>Placebo</td>
<td>5.49 (0.00,10.00)</td>
<td>9.45 (5.00,15.00)</td>
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<tr>
<td>P value</td>
<td>0.076</td>
<td>&lt;0.001</td>
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