Meta-Analysis the Efficacy of Turmeric (*Curcuma domestica*) in Reducing Pain in Patients of Knee Osteoarthritis

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**ABSTRACT**

**Background:** Osteoarthritis (OA) of the knee joint has the highest prevalence among all types of rheumatic diseases. The most common symptom of knee OA is pain around the joint. Patients with OA require long treatment, especially using analgesic and anti-inflammatory drugs. Turmeric is efficacious as a pain reliever and anti-inflammatory. This study aims to estimate the magnitude of the effect of turmeric extract (*Curcuma domestica*) on pain in patients with knee OA compared to placebo and non-steroidal anti-inflammatory drugs (NSAIDs), based on the results of a number of previous similar studies.

**Subjects and Method:** This study is a systematic review and meta-analysis with the following PICO, population: patients with knee OA. Intervention: turmeric extract. Comparison: placebo and NSAIDs. Outcome: pain reduction. The articles used in this study were obtained from three databases, namely Google Scholar, Pubmed, and Science Direct. Keywords to search for articles: “Knee Osteoarthritis” OR “Knee OA” AND “Curcuma longa” OR “Curcuma domestica” OR “Turmeric extract” AND “Placebo” OR “NSAID” AND “pain” OR “visual analogue scale” OR “VASE”. The articles included are full-text with RCT study designs from 2011 to 2021. The selection of articles is carried out using PRISMA flow diagrams. Articles were analyzed using the Review Manager 5.3 application.

**Results:** A total of 15 RCT studies were selected for systematic review and meta-analysis. Data collected from 10 studies showed that patients with knee OA who received turmeric extract experienced 1.60 units lower joint pain than placebo (SMD = -1.60; 95% CI = -2.23 to -0.97; p < 0.001). Data from 5 studies showed that patients with knee OA who received turmeric extract experienced 0.06 units higher joint pain than NSAIDs. The comparison between the turmeric extract group and the NSAID group did not show any significant difference (SMD = 0.06; 95% CI = -0.10 to -0.22; p = 0.490).

**Conclusion:** Administration of turmeric extract was more effective than placebo and not inferior to non-steroidal anti-inflammatory drugs in reducing pain in patients with knee OA.

**Keywords:** osteoarthritis, turmeric, pain

**Correspondence:**

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**BACKGROUND**

Osteoarthritis (OA) is a rheumatic disease with the highest prevalence among all types of rheumatic diseases. Osteoarthritis is the second leading cause of physical disability in the world after ischemic heart disease. The global prevalence of knee OA is estimated at 16% with an incidence of 203 per 10,000
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Based on the 2018 Basic Health Research (Riskesdas) data, the average prevalence of joint disorders including OA in Indonesia is 7.3%. Most cases were diagnosed at the age of 75 years which reached 18.9% (Riskesdas, 2019).

According to Chu et al., 2014 the symptoms of knee OA can vary depending on the cause of the problem. The most common symptom of knee OA is pain around the knee joint. Swelling, stiffness, and reduced flexibility of the knee may also be associated symptoms. These symptoms can cause a decrease in quality of life.

In general, people with osteoarthritis need treatment throughout their life, especially using analgesics and anti-inflammatory drugs, because there is no cure for it and the disease is chronic. Oral non-steroidal anti-inflammatory drugs (NSAIDs) or non-steroidal anti-inflammatory drugs (NSAIDs) are only able to suppress inflammation and pain but are not able to inhibit the course of OA disease (Adatia et al., 2012).

The curcumin in turmeric has analgesic and anti-inflammatory activity. The analgesic and anti-inflammatory activities of curcumin include inhibition of cyclooxygenase, lipoxygenase and antioxidants. The ability of curcumin has been shown to be quite strong in suppressing the activity of the cyclooxygenase enzyme as evidenced by the inhibition of arachidonic acid metabolism into prostaglandin E2 (PG-E2) and prostaglandin F2α (PG-F2α) which are dose dependent (Pinzon and Sanyasi, 2018).

Based on this background, a comprehensive study is needed from various primary studies on the effect of giving turmeric extract on pain in patients with knee osteoarthritis compared to placebo or non-steroidal anti-inflammatory drugs, based on the results of a number of previous similar studies.

**SUBJECTS AND METHOD**

1. **Study Design**
   This was a systematic review and meta analysis. The articles used in this study were obtained from several databases, namely Google Scholar, Pubmed, and Science Direct between 2011 and 2021. The selection of articles was carried out using PRISMA flow diagrams. Keywords to search for articles were as follows “Knee Osteoarthritis” OR “Knee OA” AND “Curcuma longa” OR “Curcuma domestica” OR “Turmeric extract” OR “turmeric” AND “Placebo” OR “NSAID” AND “pain” OR “ visual analogue scale” OR “VAS”.

2. **Inclusion Criteria**
   The inclusion criteria in this research article were: full-text articles using an RCT study design, the research subjects were patients with knee osteoarthritis, the intervention was turmeric extract orally, the research outcome was joint pain, English or Indonesian articles.

3. **Exclusion Criteria**
   The exclusion criteria in this research article were: articles published in languages other than English and Indonesian, studies other than RCTs, articles before 2011.

4. **Operational Definition of Variable**
   The search for articles was carried out by considering the eligibility criteria determined using the PICO model. Population: patients with knee OA. Intervention: turmeric extract. Comparison: placebo and NSAIDs. Outcome: pain reduction.

**Turmeric extract** is defined as the active compound from the turmeric plant simplicia which is given orally. The measurement scale is continuous.
Pain in patients with OA is an unpleasant sensory and emotional experience due to tissue damage to the knee joint due to OA. The instrument used is the Visual Analogue Scale score. The measurement scale is continuous.

5. Instrument Study
The research is guided by PRISMA flow diagrams and quality assessment using Critical Appraisal Tools Randomized Controlled Trials (RCT) published by CEBM University of OXFORD.

6. Data Analysis
The data in the study were analyzed using the Review Manager application (RevMan 5.3). Forest plots and funnel plots were used to determine the size of the relationship and heterogeneity of the data. A fixed effect model was used for homogeneous data, while a random effect model was used for heterogeneous data across studies.

RESULTS
The article search process is carried out through several journal databases. The review process for related articles can be seen in the PRISMA flow diagram in figure 1. Research related to the effect of turmeric extract on joint pain in knee OA consists of 10 articles with placebo comparisons and 5 articles with NSAID comparisons.

Research articles come from four continents, namely America (Brazil), Europe (Belgium), Australia and Asia (India, Iran, Thailand, Indonesia). There are 12 articles with research locations taken in the Asian continent. On the Continent of Europe, Australia and South America there is 1 article each.

Table 1, the researchers conducted an assessment of the quality of the study. Quality assessment uses Critical Appraisal Tools for Randomized Controlled Trials (RCT) published by CEBM University of OXFORD. Each assessment criterion is given a score of one if yes and the category of assessment results from the total score is 6-11 strong, 4-5 medium and 3 weak. Table 2 shows that 10 articles from RCT studies as evidence of the association of the effect of turmeric extract on joint pain in patients with knee OA with a placebo comparison. Table 3 shows 5 articles from RCT studies as evidence of the association of the effect of turmeric extract on joint pain in knee OA patients with NSAID comparisons.

Based on the results of the forest plot RCT study, the efficacy of turmeric extract (Curcuma domestica) on pain in patients with knee OA using a placebo as a comparison showed that turmeric extract was effective in reducing pain in patients with osteoarthritis (OA) knee joints.

Patients with knee OA who received turmeric extract experienced 1.60 units lower joint pain than patients with knee OA who received a placebo (Standardized Mean Difference = -1.60; 95% CI = -2.23 to -0.97; p<0.001). The heterogeneity of the research data shows $I^2 = 93\%$ so that the distribution of the data is declared heterogeneous (random effect model).

The results of the funnel plot show that there is a publication bias in the form of overestimation of the effect of turmeric in reducing pain. The plot on the right of the graph appears to have a standard error (SE) between 0.1 and 0.4. The plot on the left of the graph appears to have a standard error (SE) between 0.2 and 0.6.

Based on the results of the forest plot RCT study, the efficacy of turmeric extract (Curcuma domestica) on pain in patients with knee OA who used NSAIDs as a comparison showed that both turmeric extract and NSAIDs were effective in reducing pain in patients with knee OA. Patients with knee OA who received turmeric extract experienced 0.06 units higher joint pain than patients with knee OA who received NSAIDs.
(Standardized Mean Difference = 0.06; 95% CI= -0.10 to -0.22; p=0.490). The heterogeneity of the research data shows $I^2 = 0\%$ so that the distribution of the data is declared homogeneous (fixed effect model).

The funnel plot results show that there is a publication bias in favor of NSAIDs in reducing pain. The plot on the right of the graph appears to have a standard error (SE) between 0.1 and 0.4. The plot on the left of the graph appears to have a standard error (SE) between 0.2 and 0.6.

Figure 1. PRISMA flow diagram
Table 1. Assessment of the quality of the Critical Appraisal Tools for Randomized Controlled Trials (RCT) studies

<table>
<thead>
<tr>
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<td>Does the experiment clearly address the clinical problem?</td>
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<td>Was the intervention given to the patient randomized?</td>
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<td>3</td>
<td>Are patients, health workers, and researchers blinded?</td>
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<td>4</td>
<td>Were the study groups similar at the start of the study?</td>
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<td>Outside of the intervention under study, were the study groups treated equally?</td>
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<td>6</td>
<td>Were all patients included in the study properly accounted for in the conclusions? Were all patients analyzed according to the randomized study groups?</td>
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<td>Is the effect of the intervention large enough?</td>
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<td>How precise is the estimation of the effect of the intervention?</td>
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<td>9</td>
<td>Are the results applicable to the context of practice or local populations?</td>
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<td>Are all other clinically important outcomes considered in this article?</td>
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<td>Does the experiment clearly address the clinical problem?</td>
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</tbody>
</table>

Total: 11 11 9 11 10

Note:
1: Yes; 0: No
### Table 2. Description of the primary studies included in the meta-analysis of the primary studies by comparison with placebo

<table>
<thead>
<tr>
<th>No</th>
<th>Author (year)</th>
<th>Year</th>
<th>Study Design</th>
<th>Sample Intervention</th>
<th>Sample Control</th>
<th>P Population</th>
<th>I Intervention</th>
<th>C Comparison</th>
<th>O Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Wang et al., 2020</td>
<td>Australia</td>
<td>RCT</td>
<td>36</td>
<td>34</td>
<td>Knee OA patient, age &gt;40, VAS&gt;40</td>
<td>Turmeric Extract 500 mg 2x a day</td>
<td>placebo</td>
<td>Pain / Visual Analogue Scale (VAS) I: Mean = -23.75; SD = 18.44 C: Mean = -14.64; SD = 18.34</td>
</tr>
<tr>
<td>2</td>
<td>Hashemzadeh et al., 2019</td>
<td>Iran</td>
<td>RCT</td>
<td>40</td>
<td>40</td>
<td>Knee OA patients according to ARA criteria</td>
<td>C. domestica nano extract 40 mg 2x a day</td>
<td>placebo</td>
<td>Pain / Visual Analogue Scale (VAS) I: Mean = -9.53; SD = 4.87 C: Mean = 1.71; SD = 4.31</td>
</tr>
<tr>
<td>3</td>
<td>Atabaki et al., 2020</td>
<td>Iran</td>
<td>RCT</td>
<td>15</td>
<td>15</td>
<td>Patients with OA (age 40-55 years), VAS pain score &gt; 5</td>
<td>Turmeric Extract 80 mg 1x a day</td>
<td>placebo</td>
<td>Pain / Visual Analogue Scale (VAS) I: Mean = -4.50; SD = 1.30 C: Mean = 0.60; SD = 1.70</td>
</tr>
<tr>
<td>4</td>
<td>Henrotin et al., 2019</td>
<td>Belgium</td>
<td>RCT</td>
<td>54 &amp; 49</td>
<td>47</td>
<td>Primary femorotibial knee OA 40-85 years, pain score &gt; 40 mm in</td>
<td>C. Longa Extract 93 mg twice a day and C. Longa Extract 93 mg 3 times a day</td>
<td>placebo</td>
<td>Pain / Visual Analogue Scale (VAS) I: Mean = -12.30; SD = 19.40 C: Mean = -10.80; SD = 16.50</td>
</tr>
<tr>
<td>5</td>
<td>Panda et al., 2018</td>
<td>India</td>
<td>RCT</td>
<td>25</td>
<td>5</td>
<td>Knee OA patient, 40-75 years old, Moderate degree</td>
<td>Curene (Saffron Extract 500 mg 1 x daily)</td>
<td>placebo</td>
<td>Pain / Visual Analogue Scale (VAS) I: Mean = -25.11; SD = 8.66 C: Mean = -7.97; SD = 5.29</td>
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<tr>
<td>6</td>
<td>Srivastava et al., 2016</td>
<td>India</td>
<td>RCT</td>
<td>78</td>
<td>82</td>
<td>Knee OA patients aged 40-80 years according to ARA criteria</td>
<td>Turmeric Extract 500 mg 2 times a day</td>
<td>placebo</td>
<td>Pain / Visual Analogue Scale (VAS) I: Mean = -3.91; SD = 1.0 C: Mean = -2.55; SD = 1.27</td>
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<tr>
<td>7</td>
<td>Nakagawa et al., 2014</td>
<td>Japan</td>
<td>RCT</td>
<td>25</td>
<td>25</td>
<td>Primary medial knee OA &gt; 40 years with a Kellgren-Lawrence II or III score</td>
<td>Turmeric Extract 540 mg 2x a day</td>
<td>placebo</td>
<td>Nyeri / Visual Analogue Scale (VAS) I: Mean = -4.0; SD = 2.20 C: Mean = -2.4; SD = 2.30</td>
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<td>8</td>
<td>Panahi et al., 2014</td>
<td>Iran</td>
<td>RCT</td>
<td>27</td>
<td>26</td>
<td>Knee OA patients aged &lt;80 years. Patients with VAS &gt; 40</td>
<td>Turmeric Extract 500 mg 3x a day</td>
<td>placebo</td>
<td>Nyeri / Visual Analogue Scale (VAS) I: Mean = -3.80; SD = 2.10 C: Mean = 0.30; SD = 0.80</td>
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<td>9</td>
<td>Madhu, et al., 2013</td>
<td>India</td>
<td>RCT</td>
<td>30</td>
<td>30</td>
<td>Knee OA patient. Pain duration at least 6 months</td>
<td>Turmeric Extract 500 mg 2x a day</td>
<td>placebo</td>
<td>Nyeri / Visual Analogue Scale (VAS) I: Mean = -47.20; SD = 19.65 C: Mean = 15.47; SD = 18.35</td>
</tr>
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<td>10</td>
<td>Moharamzad et al., 2011</td>
<td>Iran</td>
<td>RCT</td>
<td>35</td>
<td>32</td>
<td>Knee OA patient, VAS pain &gt; 40</td>
<td>Turmeric Extract 600 mg 1x a day</td>
<td>placebo</td>
<td>Nyeri / Visual Analogue Scale (VAS) I: Mean = -13.70; SD = 3.50 C: Mean = -1.50; SD = 0.4</td>
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</table>
Table 3. Description of primary studies included in the primary study meta-analysis with comparison of NSAIDs

<table>
<thead>
<tr>
<th>No</th>
<th>Author</th>
<th>Place</th>
<th>Study Design</th>
<th>Total of Sample</th>
<th>P Population</th>
<th>I Intervention</th>
<th>C Comparison</th>
<th>O Outcome</th>
</tr>
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<tr>
<td>1</td>
<td>Gomes et al., 2021</td>
<td>Brazil</td>
<td>RCT</td>
<td>8</td>
<td>Knee OA patient, age &gt;40, diagnosis based on ARA criteria</td>
<td>Turmeric Extract 500 mg 2x a day</td>
<td>Ibuprofen 600 mg 2 times a day</td>
<td>Pain / Visual Analogue Scale (VAS) I: Mean= -3.0 + 2.67 C: Mean= -5.0 + 2.07</td>
</tr>
<tr>
<td>2</td>
<td>Shep et al., 2019</td>
<td>India</td>
<td>RCT</td>
<td>74</td>
<td>Knee OA patients diagnosed according to ARA criteria</td>
<td>Turmeric extract 500 mg 3 times a day</td>
<td>Diclofenac sodium 50 mg 2 times a day</td>
<td>Nyeri / Visual Analogue Scale (VAS) I: Mean= 22 + 8.10 C: Mean= 22 + 6.10</td>
</tr>
<tr>
<td>3</td>
<td>Gupte et al., 2019</td>
<td>India</td>
<td>RCT</td>
<td>22</td>
<td>Patients with OA (age 40-55 years)</td>
<td>Turmeric Extract 80 mg 1x a day</td>
<td>Ibuprofen 400 mg once a day</td>
<td>Nyeri / Visual Analogue Scale (VAS) I: Mean= -51 + 19.09 C: Mean= -55 + 16.52</td>
</tr>
<tr>
<td>4</td>
<td>Kuptnira et al., 2014</td>
<td>Thailand</td>
<td>RCT</td>
<td>171</td>
<td>Femorotibial knee OA 40-85 years, pain score &gt; 40mm Visual (VAS)</td>
<td>Turmeric extract 500 mg 3 times a day</td>
<td>Diclofenac sodium 50 mg 2 times a day</td>
<td>Nyeri / Visual Analogue Scale (VAS) I: Mean= -2.05 + 1.97 C: Mean= -2.23 + 1.86</td>
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<tr>
<td>5</td>
<td>Kertia et al., 2012</td>
<td>Indonesia</td>
<td>RCT</td>
<td>39</td>
<td>Knee OA patient, 40-75 years old, Moderate degree</td>
<td>Turmeric extract 30 mg 3 times a day</td>
<td>Diclofenac sodium 25 mg 3 times a day</td>
<td>Nyeri / Visual Analogue Scale (VAS) I: Mean= -33.77 + 22.94 C: Mean= -29.54 + 21.53</td>
</tr>
</tbody>
</table>
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**Figure 2.** The efficacy of turmeric extract (*Curcuma domestica*) on pain in patients with Knee OA who used a placebo as a comparison

**Figure 3.** Funnel Plot of the efficacy of turmeric extract (*Curcuma domestica*) on pain in patients with OA of the Knee Joint who used a placebo as a comparison
DISCUSSION

Turmeric is reported to be effective as an alternative treatment in reducing pain in OA. This study is a systematic review and meta-analysis that aims to find a conclusion from the results of various similar studies that tested the administration of turmeric extract in reducing pain in patients with knee OA in various countries, races, and ethnicities, so that conclusions can be obtained that can generally be used as a basis for the giving.

Many studies have considered turmeric extract in reducing joint pain in knee OA, this is an alternative to NSAIDs, although this drug can provide effective pain relief for OA, the use of this drug also has serious side effects after long-term conventional therapy. The side effects of chronic NSAID use are quite large, such as impaired renal function and gastrointestinal bleeding limiting their use in the treatment of knee OA (Cooper et al., 2019; Matsui et al., 2011; Teymouri et al., 2019).
1. Turmeric extract compared to placebo
Based on the results of the analysis of the primary research article, it showed that turmeric extract was effective in reducing joint pain in patients with knee OA. Patients with knee OA who received turmeric extract experienced 1.60 units lower joint pain than patients with knee OA who received placebo (Standardized Mean Difference = -1.60; 95% CI = -2.23 to -0.97; p<0.001). There were 7 primary studies that showed significant value in turmeric extract study in reducing joint pain in patients with OA of the knee joint which was indicated by not touching the horizontal line of each study with the vertical line on the forest plot. This significant value is influenced by several factors, including in the seven primary study groups the average value in the experimental group is smaller than the control group so that the cumulative SMD leads to intervention.

2. Turmeric extract compared to NSAIDs
Research related to the effectiveness of turmeric extract in reducing pain in patients with knee OA compared to non-steroidal anti-inflammatory drugs (NSAIDs/NSAIDs) consisted of 5 articles from India, Brazil, Thailand and Indonesia.

Based on the results of the analysis of 5 articles regarding the effectiveness of turmeric extract in reducing pain in patients with knee OA compared to non-steroidal anti-inflammatory drugs, it was reported that there was high homogeneity between experiments. The heterogeneity of the research data shows $I^2 = 0\%$ so that the distribution of the data is declared homogeneous (fixed effect model). Homogeneity was seen in the study population of OA patients with almost the same age and sex, the comparison was in the form of NSAIDs which had the same type and dose range, and almost the same level of pain.

Based on the results of the analysis showed that turmeric extract was not inferior to non-steroidal anti-inflammatory drugs in reducing pain in patients with knee OA. Patients with knee OA who received turmeric extract experienced 0.06 units higher joint pain than patients with knee OA who received NSAIDs (Standardized Mean Difference= 0.06; 95% CI= -0.10 to -0.22; p= 0.490). Comparison of pain in the turmeric extract group and the NSAID group showed a decrease in pain as measured by the Visual Analogue Scale (VAS) score in both groups. However, the comparison between the turmeric extract group and the NSAID group did not show a significant difference.

3. The activity of turmeric extract in reducing pain
Turmeric rhizome contains, among others, 3-4% curcuminooids (consisting of curcumin, demethoxy curcumin and bisdemethoxy curcumin), essential oils as much as 2-5% (consisting of sesquiterpenes and phenylpropene derivatives), arabinose, fructose, glucose, starch, tannins and minerals, namely magnesium, manganese, iron, copper, calcium, sodium, potassium, lead, zinc, cobalt, aluminum and bismuth (Lee et al., 2013; Sharifi-Rad et al., 2020).

Turmeric activity in reducing pain in patients with knee joint OA, through the following mechanisms: a) Decreased inflammatory response: Three components of curcuminooids, namely curcumin, demethoxy curcumin and bisdemethoxy curcumin. In vitro curcumin inhibits the activity of phospholipase, lipoxygenase, cyclooxygenase-2, leukotrienes, prostaglandins, thromboxane, NO, collagenase, elastase, hyaluronidase, interferon, TNF- and IL-12 (Verma et al., 2018; Srivastava et al., 2016; Kendra et al., 2018) b) Inhibition of monocytes from activating COX 2: Curcumin is able to inhibit the activity of cyclooxygenase enzymes,
lipoxigenases and as antioxidants. Vitro studies have shown that curcumin is able to inhibit the production of tumor necrosis factor-alpha (TNF-α) and interleukin-1 (IL-1) by human monocytes stimulated by lipopolysaccharide (Verma et al., 2018). c) Inhibition of prostaglandin synthesis: Curcumin in turmeric extract has been shown to be able to inhibit the activity of cyclooxygenase and lipoxigenase enzymes so that the production of prostaglandin E2 and leukotrienes B4 and C4 is inhibited (Choi et al., 2019; Daily et al., 2016).

In the end, it can be concluded that giving turmeric extract is more effective than placebo and not inferior to non-steroidal anti-inflammatory drugs in reducing pain in patients with knee osteoarthritis. The limitations of this study are the publication bias shown in the funnel plot and language bias because it only uses Indonesian and English articles.

AUTHOR CONTRIBUTION
Danang Ardiyanto is the main researcher who chooses topics, searches for and collects research data. Didik Gunawan Tamtomo and Bhisma Murti analyzed data and reviewed research documents.

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There is no conflict of interest in this study.

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