

## 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

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### Cite this as:

Ardiyanto D, Tamtomo DG, Murti B (2021). Meta-Analysis the Efficacy of Turmeric (*Curcuma domestica*) in Reducing Pain in Patients of Knee Osteoarthritis. Indones J Med. 06(04): 364-376. <https://doi.org/10.26911/theijmed.2021.06.04.02>.



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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

person/year (Cui et al., 2020). 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 E<sub>2</sub> (PG-E<sub>2</sub>) and prostaglandin F<sub>2α</sub> (PG-F<sub>2α</sub>) 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 joint OA. This study aims to estimate the magnitude of the effect of giving turmeric extract (*Curcuma domestica*) 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).

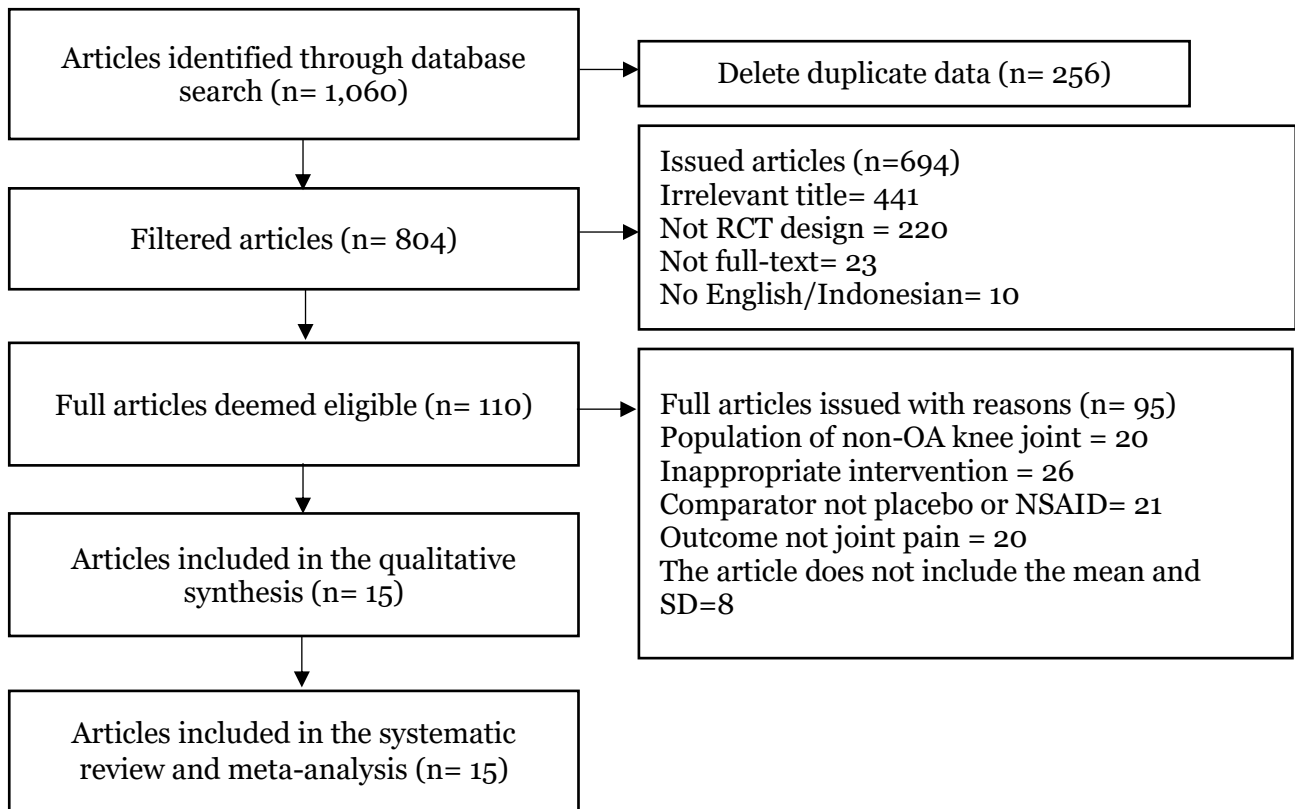
The results of the funnel plot show that there is a publication bias in the form of overestimation of the effect of turmeric in reducing pain. The plot on the right of the graph appears to have a standard error (SE) between 0.1 and 0.4. The plot on the left of the graph appears to have a standard error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

No	Rating Indicator	Publication (Author and Year)														
		Wang et al (2020)	Hashemzadeh et al (2020)	Atabaki et al (2020)	Panda et al (2018)	Srivastava et al (2016)	Nakagawa et al (2014)	Panahi et al (2014)	Henrotin et al (2019)	Madhu et al (2013)	Moharamzad et al (2011)	Gomes et al (2021)	Shepet al (2019)	Gupte et al (2019)	Kuptnira et al (2014)	Kertia et al (2012)
1	Does the experiment clearly address the clinical problem?	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
2	Was the intervention given to the patient randomized?	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
3	Are patients, health workers, and researchers blinded?	1	1	1	1	0	1	1	1	0	1	1	0	1	1	1
4	Were the study groups similar at the start of the study?	1	1	1	1	1	1	1	1	0	1	1	0	1	1	1
5	Outside of the intervention under study, were the study groups treated equally?	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
6	Were all patients included in the study properly accounted for in the conclusions? Were all patients analyzed according to the randomized study groups?	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
7	Is the effect of the intervention large enough?	1	1	0	1	1	1	1	1	1	0	0	1	0	1	1
8	How precise is the estimation of the effect of the intervention?	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1
9	Are the results applicable to the context of practice or local populations?	1	1	0	1	1	1	1	1	1	1	0	1	0	1	1
10	Are all other clinically important outcomes considered in this article?	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
11	Does the experiment clearly address the clinical problem?	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	<b>Total</b>	11	11	9	11	10	11	11	11	9	9	9	9	9	11	11

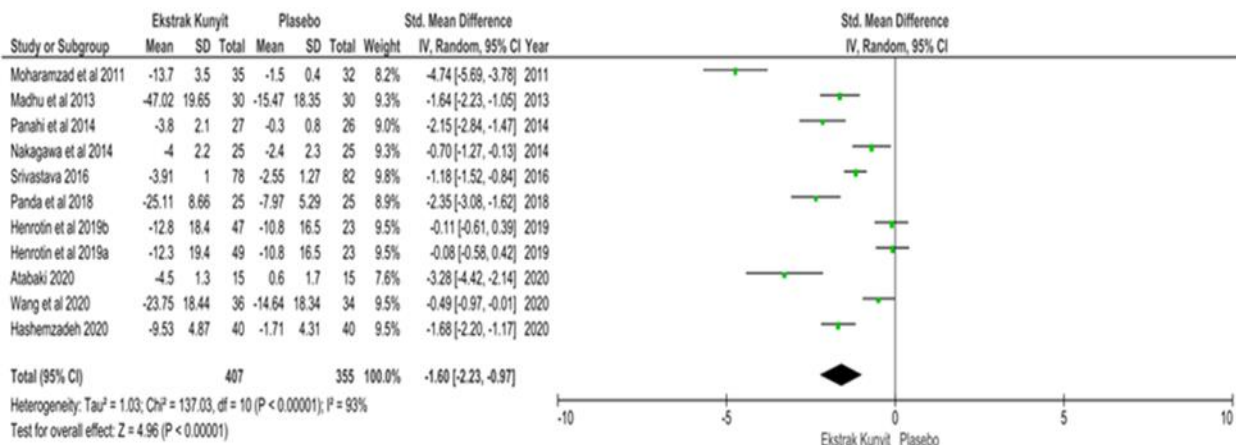
Note:  
1: Yes; 0: No

**Table 2. Description of the primary studies included in the meta-analysis of the primary studies by comparison with placebo**

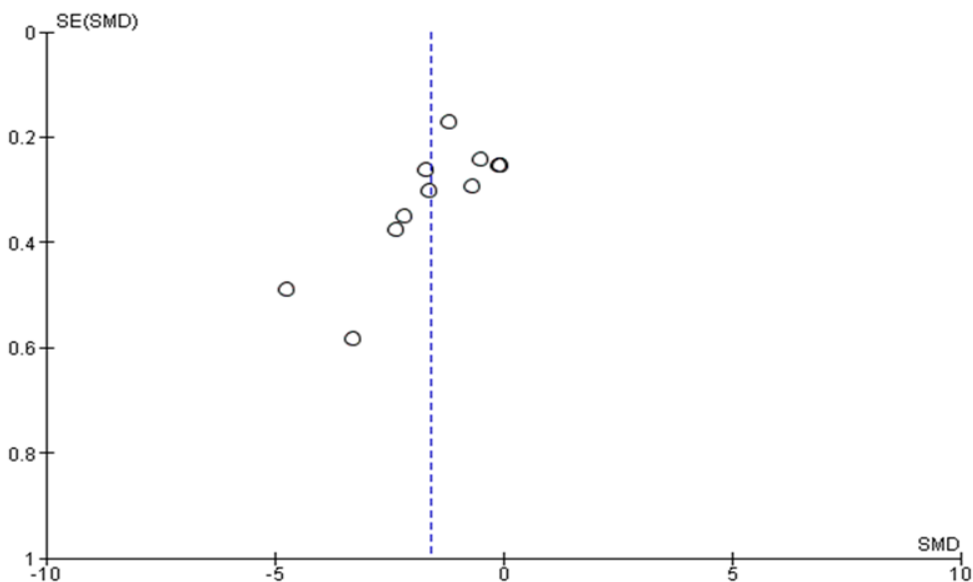
No	Author (year)	Year	Study Design	Sample		P Population	I Intervention	C Comparison	O Outcome
				Inter-vention	Con-trol				
1	Wang <i>et al.</i> , 2020	Australia	RCT	36	34	Knee OA patient, age >40, VAS>40	Turmeric Extract 500 mg 2x a day	placebo	Pain / Visual Analogue Scale (VAS) I: Mean= -23.75; SD= 18.44 C: Mean= -14.64; SD= 18.34
2	Hashemzadeh <i>et al.</i> , 2019	Iran	RCT	40	40	Knee OA patients according to ARA criteria	C. domestica nano extract 40 mg 2x a day	placebo	Pain / Visual Analogue Scale (VAS) I: Mean= -9.53; SD= 4.87 C: Mean= 1.71; SD= 4.31
3	Atabaki <i>et al.</i> , 2020	Iran	RCT	15	15	Patients with OA (age 40-55 years), VAS pain score > 5	Turmeric Extract 80 mg 1x a day	placebo	Pain/ Visual Analogue Scale (VAS) I: Mean= -4.50; SD= 1.30 C: Mean= 0.60; SD= 1.70
4	Henrotin <i>et al.</i> , 2019	Belgia	RCT	54&49	47	Primary femorotibial knee OA 40-85 years, pain score > 40mm in	C. Longa Extract 93 mg twice a day and C. Longa Extract 93 mg 3 times a day	placebo	a) Pain / Visual Analogue Scale (VAS) I: Mean= -12.30; SD= 19.40 C: Mean= -10.80; SD= 16.50 b) Pain / Visual Analogue Scale (VAS) I: Mean= -12.80; SD= 18.40 C: Mean= -10.80; SD= 16.50
5	Panda <i>et al.</i> , 2018	India	RCT	25	5	Knee OA patient, 40-75 years old, Moderate degree	Curene (Saffron Extract 500 mg 1 x daily)	placebo	Pain/ Visual Analogue Scale (VAS) I: Mean= -25.11; SD= 8.66 C: Mean= -7.97; SD= 5.29
6	Srivastava <i>et al.</i> , 2016	India	RCT	78	82	Knee OA patients aged 40-80 years according to ARA . criteria	Turmeric Extract 500 mg 2 times a day	placebo	Pain/ Visual Analogue Scale (VAS) I: Mean= -3.91; SD= 1.0 C: Mean= -2.55; SD= 1.27
7	Nakagawa <i>et al.</i> , 2014	Jepang	RCT	25	25	Primary medial knee OA > 40 years with a Kellgren-Lawrence II or III . score	Turmeric Extract 540 mg 2x a day	placebo	Nyeri / Visual Analogue Scale (VAS) I: Mean= -4.0; SD= 2.20 C: Mean= -2.4; SD= 2.30
8	Panahi <i>et al.</i> , 2014	Iran	RCT	27	26	Knee OA patients aged <80 years. Patients with VAS > 40	Turmeric Extract 500 mg 3x a day	placebo	Nyeri / Visual Analogue Scale (VAS) I: Mean= -3.80; SD= 2.10 C: Mean= -0.30; SD= 0.80
9	Madhu, <i>et al.</i> , 2013	India	RCT	30	30	Knee OA patient. Pain duration at least 6 months	Turmeric Extract 500 mg 2x a day	placebo	Nyeri / Visual Analogue Scale (VAS) I: Mean= -47.20; SD= 19.65 C: Mean= 15.47; SD= 18.35
10	Moharamzad <i>et al.</i> , 2011	Iran	RCT	35	32	Knee OA patient, VAS pain >40	Turmeric Extract 600 mg 1x a day	placebo	Nyeri / Visual Analogue Scale (VAS) I: Mean= -13.70; SD= 3.50 C: Mean= -1.50; SD= 0.4

**Table 3. Description of primary studies included in the primary study meta-analysis with comparison of NSAIDs**

No	Author	Place	Study Design	Total of Sample		P Population	I Intervention	C Comparison	O Outcome
				Intervention	Control				
1	Gomes <i>et al.</i> , 2021	Brazil	RCT	8	7	Knee OA patient, age >40, diagnosis based on ARA kriteria criteria	Turmeric Extract 500 mg 2x a day	Ibuprofen 600 mg 2 times a day	Pain / Visual Analogue Scale (VAS) I: Mean= -3.0 + 2.67 C: Mean=-5.0 + 2.07
2	Shep <i>et al.</i> , 2019	India	RCT	74	75	Knee OA patients diagnosed according to ARA . criteria	Turmeric extract 500 mg 3 times a day	Diclofenac sodium 50 mg 2 times a day	Nyeri / Visual Analogue Scale (VAS) I: Mean= 22 + 8.10 C: Mean= 22 + 6.10
3	Gupte <i>et al.</i> , 2019	India	RCT	22	27	Patients with OA (age 40-55 years)	Turmeric Extract 80 mg 1x a day	Ibuprofen 400 mg once a day	Nyeri / Visual Analogue Scale (VAS) I: Mean= -51 + 19.09 C: Mean= -55 + 16.52
4	Kuptnira tsaikul <i>et al.</i> , 2014	Thailand	RCT	171	160	Femorotibial knee OA 40-85 years, pain score > 40mm visual (VAS)	Turmeric extract 500 mg 3 times a day	Diclofenac sodium 50 mg 2 times a day	Nyeri / Visual Analogue Scale (VAS) I: Mean= -2.05 + 1.97 C: Mean= -2.23 + 1.86
5	Kertia <i>et al.</i> , 2012	Indonesia	RCT	39	41	Knee OA patient, 40-75 years old, Moderate degree	Turmeric extract 30 mg 3 times a day	Diclofenac sodium 25 mg 3 times a day	Nyeri / Visual Analogue Scale (VAS) I: Mean= -33.77 + 22.94 C: Mean= -29.54 + 21.53

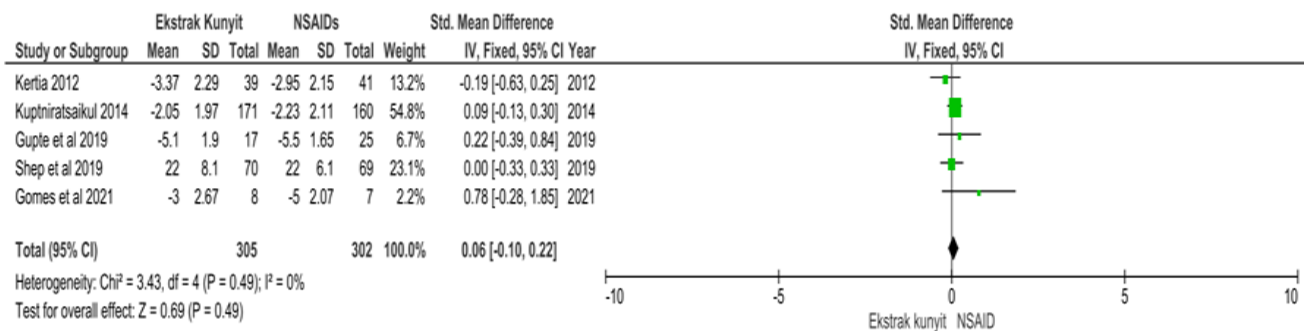


**Figure 2. The efficacy of turmeric extract (*Curcuma domestica*) on pain in patients with Knee OA who used a placebo as a comparison**

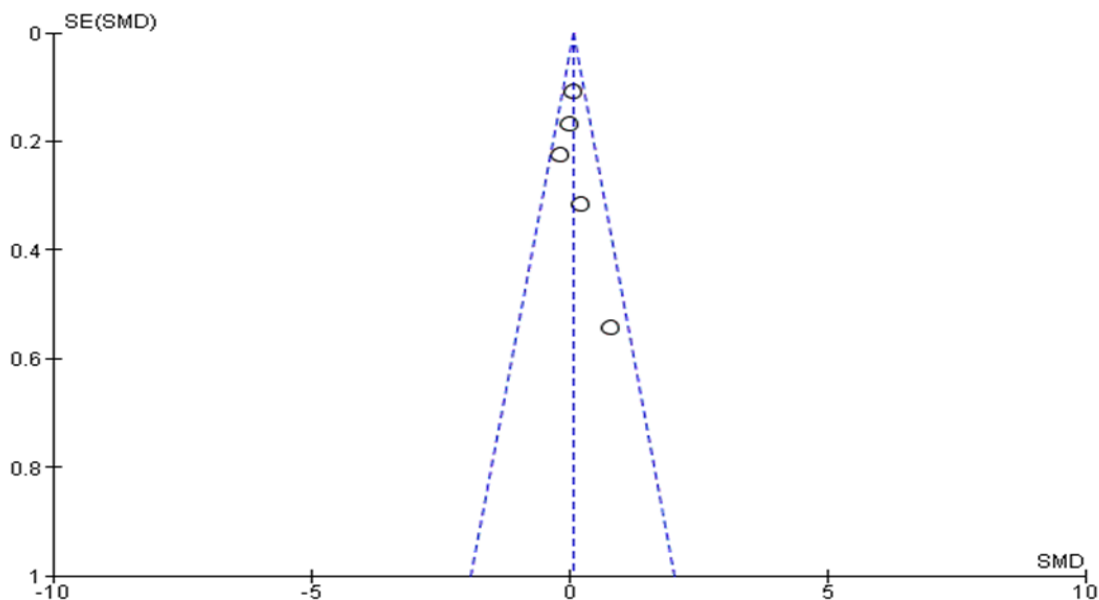


**Figure 3. Funnel Plot of the efficacy of turmeric extract (*Curcuma domestica*) on pain in patients with OA of the Knee Joint who used a placebo as a comparison**





**Figure 4. Forest plot of the efficacy of turmeric extract (*Curcuma domestica*) on pain in patients with OA of the knee joint using NSAIDs as a comparison**



**Figure 5. Funnel plot of the efficacy of turmeric extract (*Curcuma domestica*) on pain in patients with knee joint osteoarthritis using NSAIDs 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% curcuminoids (consisting of curcumin, demethoxy curcumin and bisdemethoxy curcumin), essential oils as much as 2-5% (consisting of sesquiterpenes and phenylpropane 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 curcuminoids, 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,

lipoxygenases and as antioxidants. Vitro studies have shown that curcumin is able to inhibit the production of tumor necrosis factor-alpha (TNF- $\alpha$ ) 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 lipoxygenase 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.

#### **FUNDING AND SPONSORSHIP**

This study is self-funded.

#### **CONFLICT OF INTEREST**

There is no conflict of interest in this study.

#### **ACKNOWLEDGEMENT**

We thank the database providers Google Scholar, Pubmed, and Science Direct.

#### **REFERENCES**

Adatia A, Rainsford KD, Kean, WF (2012). Osteoarthritis of the knee and hip. Part I: aetiology and pathogenesis as a basis

for pharmacotherapy. *J Pharm Pharmacol.* 64(5):617–625. doi.org/10.1111/J.20427158.2012.01458.X.

Atabaki M, Shariati-Sarabi Z, Tavakkol-Afshari J, Mohammadi M (2020). Significant immunomodulatory properties of curcumin in patients with osteoarthritis; a successful clinical trial in Iran. *Int Immunopharmacol.* 85 (4): 596-607. <https://doi.org/10.1016/j.intimp.2020.106607>.

Choi Y, Ban I, Lee H, Baik M (2019). Puffing as a novel process to enhance the antioxidant and anti-inflammatory properties of *Curcuma longa L.* (turmeric). *Mdpi.Com.* <https://doi.org/10.3390/antiox8110506>.

Chu CR, Millis MB, Olson, SA (2014). Osteoarthritis: From palliation to prevention AOA critical issues. *J Bone Joint Surg Am.* 96(15): 130-135. <https://doi.org/10.2106/JBJS.M.01209>.

Cooper C, Chapurlat R, Al-Daghri, N, Herero-Beaumont G, Bruyère O, Rannou F, Roth R, et al. (2019). Safety of oral non-selective non-steroidal anti-inflammatory drugs in osteoarthritis: what does the literature say?. *Drugs Deliv.* 36(1): 15–24. <https://doi.org/10.1007/s40266-019-00660-1>.

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. *E Clinical Medicine.* (1): 29-33. <https://doi.org/10.1016/j.eclinm.2020.100587>.

Daily JW, Yang M, Park S (2016). Efficacy of turmeric extracts and curcumin for alleviating the symptoms of joint arthritis: a systematic review and meta-analysis of randomized clinical trials. *J Med Food.* 19(8):717–729. <https://doi.org/10.1089/jmf.2016.3705>.

- Gomes TP, Souza JIN, Somerlate LC, Mendonça VA, Lima NM, Carli GP, Castro SBR, et al. (2021). Miconia albicans and Curcuma longa herbal medicines positively modulate joint pain, function and inflammation in patients with osteoarthritis: a clinical study. *Inflammopharmacology*. 29(2):377–391. doi.org/10.1007/s10787-020-00781-9.
- Gupte PA, Giramkar SA, Harke SM, Kulkarni SK, Deshmukh AP, Hingorani L, Mahajan MP, Bhalerao SS (2019). Evaluation of the efficacy and safety of capsule longvida® optimized curcumin (solid lipid curcumin particles) in knee osteoarthritis: A pilot clinical study. *J Inflamm Res*. (12):145–152. doi.org/10.2147/JIR.S205390.
- Hashemzadeh K, Davoudian N, Jaafari MR, Mirfeizi Z (2019). The Effect of Nano-curcumin in Improvement of Knee Osteoarthritis: A Randomized Clinical Trial. *Curr Rheumatol Rev*. (2):158–164. https://doi.org/10.2174/187447-1013666191223152658.
- Henrotin Y, Malaise M, Wittoek R, De Vlam K, Brasseur JP, Luyten F, Jiangang Q, et al. (2019). Bio-optimized Curcuma longa extract is efficient on knee osteoarthritis pain: A double-blind multicenter randomized placebo controlled three-arm study. *Arth Res Ther*. 21(1): 45-50. https://doi.org/10.1186/S130-75-019-1960-5.
- Kertia N, Asdie AH, Rochmah W, Marsetyawan (2012). Ability of curcuminoid compared to diclofenac sodium in reducing the secretion of cyclooxygenase-2 enzyme by synovial fluid's monocytes of patients with osteoarthritis. *Acta Med Indones*. 44(2): 105–113. http://www.inaactamedica.org/archives/2012/22745140.pdf.
- Kuptniratsaikul V, Dajpratham P, Chootip C, Saengsuwan J, Tantayakom K, Laongpech S (2014). Efficacy and safety of Curcuma domestica extracts compared with ibuprofen in patients with knee osteoarthritis: A multicenter study. *Clin Int Aging*. 9: 451–458. https://doi.org/10.2147/cia.s58535.
- Lee WH, Loo CY, Bebawy M, Luk F, Mason R, Rohanizadeh R. (2013). Curcumin and its Derivatives: Their Application in Neuropharmacology and Neuroscience in the 21st Century. *Cur Neuropharm*. 11(4):338–378. https://doi.org/10.2174/1570159X11311040002.
- Li L, Zhang Y, Zeng C (2020). Update on the epidemiology, genetics, and therapeutic options of hyperuricemia. *Am J of Trans Res*. 12(7): 31-37. http://www.ncbi.nlm.nih.gov/pmc/articles/pmc7407685/.
- Madhu K, Chanda K, Saji, MJ. (2013). Safety and efficacy of Curcuma longa extract in the treatment of painful knee osteoarthritis: A randomized placebo-controlled trial. *J Inflamm* 21 (2): 129–136. https://doi.org/10.1007/s10787-012-0163-3.
- Matsui H, Shimokawa O, Kaneko T, Nagano Y, Rai K, Hyodo I (2011). The pathophysiology of non-steroidal anti-inflammatory drug (NSAID)-induced mucosal injuries in stomach and small intestine. *J Clin Bio Nutri*, 48(2):107–111. https://doi.org/10.3164/JCBN-10-79.
- Nakagawa Y, Mukai S, Yamada S, Matsuoka M, Tarumi E, Hashimoto T, Tamura C, Imaizumi A, Nishihira J, Nakamura T. (2014). Short-term effects of highly-bioavailable curcumin for treating knee osteoarthritis: a randomized, double-blind, placebo-controlled prospective study. *J Ortho Sci*. 19(6):933–939. https://doi.org/10.1007/s00776-014-0633-0.
- Panahi Y, Rahimnia AR, Sharafi M, Alishiri

- G, Saburi A, Sahebkar A (2014). Curcuminoid Treatment for Knee Osteoarthritis: A Randomized Double-Blind Placebo-Controlled Trial. *Phyto Res.* 28(11): 1625–1631. <https://doi.org/10.1002/PTR.5174>.
- Panda SK, Nirvanashetty S, Parachur VA, Mohanty N, Swain T (2018). A Randomized, Double Blind, Placebo Controlled, Parallel-Group Study to Evaluate the Safety and Efficacy of Curene® versus Placebo in Reducing Symptoms of Knee OA. *Bio Med Res Int.* 20(1): 50-55. <https://doi.org/10.1155/2018/5291945>.
- Pinzon RT, Sanyasi RD (2018). Curcuma longa for Arthritis pain: Systematic review of randomized controlled trial study. *Asian J Pharm* 4(5): 528–534. <https://doi.org/10.31024/ajpp.2018.4.5.1>.
- Riskesdas (2019). Laporan hasil Riset Kesehatan Dasar (RISKESDAS) Nasional. Badan Penelitian dan Pengembangan Kesehatan Kemenkes RI. <https://www.litbang.kemkes.go.id/laporan-riset-kesehatan-dasar-riskesdas/>.
- Sharifi-Rad J, Rayess Y, El Rizk AA, Sadaka C, Zgheib R, Zam W, Sestito S, et al. (2020). Turmeric and Its Major Compound Curcumin on Health: Bioactive Effects and Safety Profiles for Food, Pharmaceutical, Biotechnological and Medicinal Applications. *Front Pharmacol.* 11(11): 1–23. <https://doi.org/10.3389/fphar.2020.01021>.
- Shep D, Khanwelkar C, Gade P, Karad S. (2019). Safety and efficacy of curcumin versus diclofenac in knee osteoarthritis: A randomized open-label parallel-arm study. *Trials.* 20 (1): 1–11.
- Srivastava S, Saksena AK, Khattri S, Kumar S, Dagur RS (2016). Curcuma longa extract reduces inflammatory and oxidative stress biomarkers in osteoarthritis of knee: a four-month, double-blind, randomized, placebo-controlled trial. *Inflammopharmacology,* 24(6): 377–388. <https://doi.org/10.1007/s10787-016-0289-9>.
- Teymouri S, Rakhshandeh H, Baghdar H, Yousefi M, Salari R (2019). Analgesic herbal medicines in the treatment of knee osteoarthritis: A systematic review. *Curr Rheumatol Rev.* 15(4): 290–303. <https://doi.org/10.2174/157339-7115666190328150203>.
- Verma RK, Kumari P, Maurya RK, Kumar V, Verma RB, Singh RK (2018). Medicinal properties of turmeric (*Curcuma longa L.*): A review. *Int J Chem Study.* 6 (4): 1354–1357. <https://www.chemjournal.com/archives/?year=2018&vol=6&issue=4&ArticleId=3186&si=false>.
- Wang Z, Jones G, Winzenberg T, Cai G, Laslett LL, Aitken D, Hopper I, Singh A, Jones R, et al. (2020). Effectiveness of Curcuma longa Extract for the Treatment of Symptoms and Effusion-Synovitis of Knee Osteoarthritis: A Randomized Trial. *Ann Int Med* 173 (11): 861–869. <https://doi.org/10.73-26/M20-0990>.