The efficacy and safety of Curcuma longa Extract and curcumin supplements on osteoarthritis: a systematic review and meta-analysis

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Abstract

Objective: To assess the efficacy and safety of Curcuma longa Extract and curcumin supplements on osteoarthritis (OA).

Methods: The databases such as Pubmed and Cochrane Library were searched to collect the article about Curcuma longa Extract and curcumin in the treatment of OA. Then, randomized controlled trials (RCTs) were selected and their data was extracted. Finally, the RevMan5.3 was utilized for risk of bias assessment and meta-analysis, the STATA15.0 were utilized for publication bias assessment, and GRADE tool were used for the evidence quality assessment of primary outcomes.

Results: A total of 15 RCTs involving 1621 participants were included. (1) Compared with placebo, Curcuma longa Extract and curcumin (C.) can decrease the VAS and WOMAC score-pain, the WOMAC score-function and the WOMAC score-stiffness. In terms of adverse events, Curcuma longa Extract and curcumin are comparable to those of placebo. (2) Compared with NSAIDs, Curcuma longa Extract and curcumin have similar effects on joint pain, function and stiffness. The incidence of adverse events in Curcuma longa Extract and curcumin was lower. (3) Compared with the NSAIDs group, C.+NSAIDs can also decrease the VAS and WOMAC score-pain, the WOMAC score-function...
and the WOMAC score-stiffness. In terms of adverse events, the addition of Curcuma longa Extract and curcumin to NSAIDs did not increase adverse events.

**Conclusion:** Curcuma longa Extract and curcumin may be a safer and effective supplement for OA patients. It is recommended to use Curcuma longa Extract and curcumin supplement for OA patients for more than 12 weeks.

**Keywords** Curcuma longa Extract; Curcumin; Osteoarthritis; Systematic review; Meta-analysis

**Conflict of Interest**

We declare no competing interests.

**1 Introduction**

With the increase in the aging population in China, the incidence of osteoarthritis (OA), a chronic degenerative disease, has increased year by year. There are more than 400 million osteoarthritis patients worldwide, and the disability rate of OA may be as high as 53% [1]. In 2016, the prevalence of symptomatic knee OA in China has reached 8.1%, and the number of patients is at least 110 million patients with knee OA [2-3]. The main pathological manifestations of OA include the destruction of articular cartilage, the formation of osteophytes, synovitis and joint space narrowing [4]. In addition, symptomatic knee OA can increase the all-cause mortality rate by nearly double, causing a great burden on medical resources and social diseases [5]. The current management of OA is mainly to evaluate the patient's pain, joint function and the patient's expected curative effect after the diagnosis of the disease, in order to develop an individualized treatment plan [6]. The main purpose of the treatment is to relieve pain, delay the progress of joint degeneration, improve or restore joint function to improve the patient's quality of life, including basic treatment, drug treatment and surgical treatment [7-9]. Among them, basic treatment helps patients recognize and change their bad living habits through health education, and encourages patients to exercise appropriately to increase muscle strength and strengthen joint stability, supplemented by physical therapy to change the local metabolic environment of the joints and relieve pain [8]. Drug treatment mostly chooses topical or oral non-steroidal anti-inflammatory drugs (NSAIDs) to relieve pain and improve joint function; oral or intra-articular injection of drugs can also be used to nourish articular cartilage and lubricate the joint cavity [9]. When non-surgical treatment is ineffective, different surgical methods are selected for patients at different disease stages.
to achieve the purpose of treatment. Among them, artificial joint replacement is an effective and mature method for treating patients with end-stage disease [9]. In the OA stepped and individualized treatment plan, oral drug treatment plays a pivotal role due to its high degree of acceptability and exact curative effect, but the adverse reactions of long-term use of NSAIDs also plague patients and clinical medical staff [10-11].

*Curcuma longa*, a rooted plant in the ginger family, has become the first choice for alternative medicine due to its anti-inflammatory, antioxidant and digestive properties. Its main ingredient, curcumin, is also a natural active oxygen scavenger and active nitrogen provider, and has been proven to be effective in treating pain caused by arthritis and OA [12]. The main mechanism may be related to the protection of IL-1B-induced apoptotic chondrocytes, improvement of early degenerative changes of articular cartilage, inhibition of the production of cytoplasmic phospholipase A2 (cPLA2), cyclooxygenase 2 (COX-2), lipoxygenase (5-LOX), etc. [12-13]. Recent clinical studies have also shown that curcumin can improve many indicators of OA. A recent meta-analysis showed that curcumin can effectively treat patients with OA, improve WOMAC score and VAS score, and its side effects are not higher than that of ibuprofen, but only 5 Randomized controlled trial (RCTs) were included, which severely limited its applicability of evidence [14]. Another meta-analysis found that curcumin and frankincense formula can relieve symptoms while reducing safety risks. It may be supplementary evidence for the treatment of knee OA, but the quality of the included RCTs is limited, and the number is too small to make it impossible to make definite clinical practice recommendations [15]. With the gradual increase of RCTs [16-20] and the accumulation of evidence, there is an urgent need to update the systematic review and meta-analysis. Therefore, this article will conduct a systematic review and meta-analysis on the efficacy and safety of curcumin intervention in OA based on the latest updated evidence.

2 Materials and Methods

2.1 Literature search strategy

This systematic review and meta-analysis were conducted strictly in accordance with PRISMA-guidelines (see supplementary materials). The Chinese databases [China Biology Medicine (CBM), China National Knowledge Infrastructure (CNKI), VIP Database for Chinese Technical Periodicals, Wanfang Database on Academic Institutions in China] were searched, and the search time range was from their establishment to Oct. 6, 2020. The English databases (Web of Science, Embase, PubMed,
MEDLINE Complete, ClinicalTrials.gov) were searched in the same way, and the search time range was from their establishment to Oct. 6, 2020. The Cochran Library were also searched (Issue 10 of 12, November 2020). The search strategy of Pubmed and Embase is shown in Table S1 as an example.

2.2 Selection criteria

2.2.1 Participants
Patients diagnosed with OA by recognized criteria. There are no restrictions on gender, age, ethnicity, etc.

2.2.2 Intervention
The intervention of the experimental group is Curcuma longa Extracts and curcumin, which can be used alone or in combination with conventional therapies. The control group was a placebo or conventional therapy.

2.2.3 Outcomes
The primary outcomes were pain [visual analogue scale (VAS) and The Western Ontario and McMaster Universities (WOMAC) score-pain], joint function (WOMAC-function), joint stiffness (WOMAC-stiffness), and adverse events. The secondary outcomes were other assessments score of OA [such as the knee injury and osteoarthritis score (KOOS) (including Function in daily living, Function in sport and recreation, Quality of life)] and biochemical indicators (such as oxidative stress indicators and COX-2 levels)

2.2.4 Study design
RCTs, with no limitations to publication time, language, quality and publication status.

2.2.5 Exclusion criteria
The exclusion criteria are: (1) Curcuma longa Extracts and curcumin combined with other unconventional therapies; (2) the participant is not human; (3) Non-original research literature.

2.3 Literature screening and data extraction
According to the research objects and methods, the literature is initially screened, and then the full text is read, and then screened again according to the above inclusion and exclusion criteria. The data of all RCTs were independently extracted by two reviewers and cross-checked. If there is a disagreement, it will be resolved through discussion by all reviewers. The extracted data include basic information (author, publication time, age of research object, etc.), sample size, intervention measures, intervention time, measurement indicators, etc.
2.4 Risk of Bias Assessment

Two reviewer independently used the Cochrane risk of bias assessment tool to evaluate the quality of RCTs, and if there were disagreements, they were discussed with all reviewer [21]. The tool includes the following six aspects: random sequence generation, allocation concealment, blinding, incomplete outcomes, selective reporting and other biases. Each item is recorded as: low risk of bias, high risk of bias, unclear risk of bias.

2.5 Statistical analysis

RevMan 5.3 was used for risk of bias assessment and meta-analysis. I² is used to test the specificity between RCTs. If there is homogeneity between RCTs (I%<50%, P>0.1), the fixed effects model is used for Meta-analysis. If there is heterogeneity between RCTs (I%>50%, P<0.1), we would first discuss the source of heterogeneity and conduct subgroup analysis. If the heterogeneity is not reduced, the random effects model is used for Meta-analysis [22]. For continuous variables, if the measurement data units are different or the values differ greatly, the standard mean difference (SMD) is used as the effect size indicator, while in other cases, the mean difference (MD) is used as the effect size indicator. For dichotomous variables, the risk ratio (RR) is used as the effect size indicator. The size of the effect is expressed with a 95% confidence interval (95% CI). The publication bias was detected by STATA 15 with Egger method (continuous variable) and Harbord methods (dichotomous variable) for primary outcomes. P>0.1 is considered to have no publication bias.

3 Results

3.1 Results of the Search

Of the 679 articles originally included, 22 articles were evaluated in detail, and finally 7 articles were excluded because they did not meet the inclusion and exclusion criteria. In the end, a total of 15 RCTs were included (Figure 1). Among the exclusion articles, 4 of them were Curcuma longa Extracts and curcumin combined with other unconventional therapies [23-26], while 2 of them were not RCTs [27-28], 1 of them was not original article [29]. The basic characteristics of each RCTs are shown in Table 1.
3.2 Description of included trials

Most of the 15 RCTs are from different countries, among which Haroyan et al. 2018 [31] comes from Armenia, Wang et al. 2020 [16] comes from Australia, Henrotin et al. 2019 [18] comes from...
Belgium, Kertia et al. 2012 [32] comes from Indonesia, and Nakagawa et al. 2014 [36] comes from Japan. In addition, 3 RCTs come from India [20, 38-39], 3 RCTs come from Thailand [33, 35, 37], and 4 RCTs come from Iran [17, 19, 30, 34]. These 15 RCTs involve a total of 1621 participants, and the scale of each RCT is 40-400 participants. There are 2 experimental groups in Henrotin et al. 2019 (high-dose group and low-dose group), so the control group is divided into 2 small subgroups accordingly, matching the high-dose group and the low-dose group respectively (Henrotin et al. 2019a and Henrotin et al. 2019b). Madhu et al. 2013 has 2 experimental groups (Curcuma longa Extract alone and Curcuma longa Extract + Glucosamine) and 2 control groups (Glucosamine and Placebo); for the convenience of comparison, we matched the data of Curcuma longa Extract with placebo (Madhu et al. 2013a), and matched the data of Curcuma longa Extract+Glucosamine with Glucosamine (Madhu et al. 2013b). The details of study characteristics are presented in Table 1.

Table 1-1 The characteristics of the included studies

| Study               | Country       | Sample size (Female/male) | Intervention                                      |
|---------------------|---------------|---------------------------|--------------------------------------------------|
| Wang et al. 2020    | Australia     | 36 (18/18) 34 (21/13)     | Curcuma longa Extract 1000 mg                     |
| Jamali et al. 2020  | Iran          | 36 (22/14) 36 (23/13)     | Curcumin ointment Placebo (Vaseline ointment)     |
| Henrotin et al. 2019| Belgium       | 96 (79/17) 45 (34/11)     | Curcuma longa Extract 280mg or 197mg             |
| Hashemzadeh et al. 2020 | Iran     | 36 (29/7) 35 (31/4)       | Curcuminoids (SinaCurcumin™) 40mg                 |
| Shep et al. 2019    | India         | 70 (48/21) 69 (45/25)     | Curcumin (BCM-95®) 1500 mg                       |
| Panahi et al. 2016  | Iran          | 19 (14/5) 21 (17/4)       | Curcuminoids (C3 complex®) 1500 mg                |
| Haroyan et al. 2018 | Armenia       | 66 (62/5) 68 (65/3)       | Curcuminoids 999mg Placebo (CuraMed® 1500mg)     |
| Kertia et al. 2012  | Indonesia     | 39 (24/15) 41 (29/12)     | Curcuminoid 90mg Diclofenac sodium 90mg           |
| Kuptniratsaikul et al. 2009 | Thailand | 52 (41/11) 55 (45/10)     | Curcuma longa Extract 2000 mg ibuprofen 800 mg    |
| Study                     | Relevant outcomes               | Mean age (years) | BMI | Duration |
|--------------------------|---------------------------------|------------------|-----|----------|
|                          |                                 | Trial group      | Control group | Trial group | Control group |
| Panahi et al. 2014 [34]  | Curcuminoid 1500mg              | 61.3±8.5         | 62.4±8.8     | 29.9±6.3   | 30.6±7.2      | 12 weeks      |
| Kuptniratsaikul et al. 2014 [35] | Curcuma longa Extract 1500 mg              | 68.86 ± 6.2      | 67.94 ± 6.7  | 27.59 ± 3.4 | 27.54 ± 3.9  | 6 weeks        |
| Nakagawa et al. 2014 [36] | Curcumin 180 mg                 | 60.9±9.78;       | 63.3±7.69;   | 29.4±4.87; | 29.4±5.2    | 12 weeks      |
| Pinsornsak et al. 2012 [37] | Curcuma longa Extract 1000 mg+  | 61.4±7.49        | 30.4±5.32    |               |              |              |
| Madhu et al. 2013 [38]   | Glucosamine 1500 mg             | 54.11±5.80       | 56.54±5.77   | -           | -           | 6 weeks        |
| Srvastava et al. 2016 [39] | Curcuma longa Extract 500 mg+D  | 53.09 ± 5.17     | -            | -           | -           |              |
| Wang et al. 2020 [16]    | VAS, WOMAC score, adverse events | 57.32 ± 5.77     | 57.57 ± 5.77 | 28.75 ± 5.77 | 28.94 ± 5.77 | 6 weeks        |
| Jamali et al. 2020 [17]  | VAS, adverse events             | 4.17             | 4.17         |              |              | 4 weeks        |
| Henrotin et al. 2019 [18]| KOOS, adverse events            | 54.65 ± 8.8      | 56.04 ± 8.5  | 28.33 ± 3.6 | 28.81 ± 3.3 | 12 weeks      |
| Hashemzadeh et al. 2020 [19] | WOMAC score, adverse events | 64.05 ± 6.46     | 64.56 ± 6.28 | 26.28 ± 4.64 | 26.44 ± 4.46 | 4 weeks        |
| Year       | Study Details | VAS, WOMAC score | VAS, adverse events | Adverse Events | Timeframe |
|------------|---------------|------------------|---------------------|----------------|-----------|
| 2012 [32] | Kuptniratsaiku l et al. 2009 [33] | 8.83 | 8.86 | 3.62 | 4.79 | 6 weeks |
| 2012 [32] | Panahi et al. 2014 [34] | 8.78 | 9.05 | 3.17 | 3.17 | 6 weeks |
| 2014 [35] | Kuptniratsaiku l et al. 2014 [35] | 57.32 ± 57.57 | ± 28.75 ± 28.75 | ± 6 weeks |
| 2014 [35] | Nakagawa et al. 2014 [36] | 71.9±5.3 | 66.1±7.2 | 25.1±2.7 | 24.8±2.3 | 8 weeks |
| 2012 [37] | Pinsornsak et al. 2012 [37] | 56.63 ± 56.80 | ± 27.01 ± 27.80 | ± 6 weeks |
| 2013 [38] | Madhu et al. 2013 [38] | 58.17 ± 9.98 | ± 5.20 ± 4.21 | ± 6 weeks |
| 2016 [39] | Srivastava et al. 2016 [39] | 50.23 ± 50.27 | ± 28.32 ± 27.40 | ± 6 weeks |
| 2012 [32] | Panahi et al. 2012 [37] | - | - | - | 12 weeks |

3.3 Risk of bias of included studies

The summary and graph of risk of bias were shown in figure 2 and 3.

3.3.1 Random Sequence generation

Three RCTs [32, 36-37] did not describe the random sequence generation methods, hence they were rated as unclear risk of bias. Other RCTs described the sequence generation methods, and were rated as low risk of bias. Among those RCTs, Panahi et al. 2016 [30] and Panahi et al. 2014 [34] utilized a 1:1 ratio scheme, Henrotin et al. 2019 [18] utilized blocking randomization, Hashemzadeh et al. 2020 [19] utilized random number table, and Jamali et al. 2020 [17] utilized the online block randomization program. The other 7 RCTs used computer software to generate random sequences.

3.3.2 Allocation concealment

Two RCTs [30, 32] did not describe whether allocation concealment was performed, and therefore were assessed as unclear risk of bias. The remaining RCTs use similar-looking drug packaging, or only
allow pharmacists to see the random number, or package the random number in a similar-looking opaque box, or use computer-generated random sequences that cannot be guessed by researchers and participants, so they were considered to be a low risk of bias.

3.3.2 Blinding

Kuptniratsaikul et al. 2009 [33] only described the blinding for outcome assessment, but failed to describe the blinding for participants and its outcomes are subjective indicators (VAS), hence it was rated as having low risk of bias in blinding of outcome assessment and having high risk of bias in blinding of participants and personnel. Madhu et al. 2013 [38] only used blinding to the participants, not blinding to the measurer, hence it was rated as having low risk of bias in blinding of participants and personnel and having high risk of bias in blinding of outcome assessment. Although the four RCTs claimed to use blinding, they did not describe the process of blinding implementation in the paper, so they were assessed as unclear risk of bias. Panahi et al. 2016 [30] and Kertia et al. 2012 [32] did not state whether blinding was used, but because its outcomes are objective indicators (such as COX-2, SOD, MDA), which is less affected by blinding; hence, we assessed the risk of bias as low. Shep et al. 2019 [20] did not mention whether to use blinding, and its main outcome indicators are subjective evaluation indicators, hence it was rated as high risk of bias. Other RCTs describe the process of blind implementation and are therefore judged as low risk of bias.

3.3.3 Incomplete outcome data and Selective reporting

Although all RCTs exist and participants fall off, because the reasons for falling out and the number of people were balanced, they were considered to be low risk of bias. No selective reports were found in all RCTs, so they were considered low risk of bias.

3.3.4 Other potential bias

Other sources of bias were not observed in 15 RCTs; therefore, the risks of other bias of the RCTs were low.
3.4 Primary outcomes

3.4.1 Pain

The improvement of pain is represented by the results of VAS and WOMAC score-pain.

(1) VAS: Although 10 RCTs reported VAS [16-18, 20, 33-34, 36-39], because the data of Nakagawa et al. 2014 [36] and Pinsornsak et al. 2012 [37] are different from other RCTs, they were not integrated for meta-analysis. These RCTs are divided into different subgroups according to their intervention group and control group: (1) Curcuma longa Extract and curcumin (C.) v.s. placebo; (2) C. v.s. NSAIDs; (3) C.+ NSAIDs v.s. NSAIDs; (4) C. +Glucosamine v.s. Glucosamine. The heterogeneity test showed that the heterogeneity of the main subgroups was high [(1): I²= 69%,
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P=0.007; (2): I2= 0%, P=0.76; (3)-(4): not applicable], so the random effects model was used for meta-analysis. The meta-analysis results of each subgroup showed that: (1) Compared with placebo, Curcuma longa Extract and curcumin can reduce VAS (WMD -11.55, 95%CI -14.3 to -9.06, P<0.00001; random effect model). (2) Compared with the NSAIDs group, there was no statistical difference in the improvement of VAS by Curcuma longa Extract and curcumin (WMD -0.34, 95%CI -1.25 to 0.57, P=0.46; random effect model); (3) Compared with the NSAIDs group, the VAS in C.+NSAIDs group was lower (WMD -1.08, 95%CI -1.12 to -1.04, P<0.00001; random effect model); (4) The difference of VAS between Glucosamine group and C.+ Glucosamine group was of no statistical significance (WMD 7.04, 95%CI -6.49 to 20.57, P=0.31; random effect model). The summary result also showed the VAS in experimental group was lower (WMD -6.23, 95%CI -10.15 to -2.31, P=0.002; random effect model). (Figure 4).

![Figure 4 The results of VAS](image_url)

(2) WOMAC score-pain: 6 RCTs reported WOMAC score-pain of patients [16-18, 20, 33-34, 38-39]. These RCTs are divided into different subgroups according to their intervention group and control group: (1) Curcuma longa Extract and curcumin (C.) v.s. placebo; (2) C. v.s. NSAIDs; (3) C.+ NSAIDs
v.s. NSAIDs. The heterogeneity test showed that the heterogeneity of the main subgroups was low [(1): I²= 34%, P=0.21; (2)-(3): not applicable], so the fixed effects model was used for meta-analysis. The meta-analysis results of each subgroup showed that: (1) Compared with placebo, Curcuma longa Extract and curcumin can reduce WOMAC score-pain (SMD -0.66, 95%CI -0.88 to -0.43, P<0.0001; fixed effect model). (2) Compared with the NSAIDs group, there was no statistical difference in the improvement of WOMAC score-pain by Curcuma longa Extract and curcumin (SMD 0.04, 95%CI -0.18 to 0.25, P=0.72; fixed effect model); (3) Compared with the NSAIDs group, the WOMAC score-pain in C.+NSAIDs group was lower (SMD -4.10, 95%CI -4.65 to -3.55, P<0.0001; fixed effect model). The summary result also showed the WOMAC score-pain in experimental group was lower (SMD -0.57, 95%CI -0.73 to -0.42, P<0.0001; fixed effect model). (Figure 5).

| Study or Subgroup | Experimental | Control | Std. Mean Difference | Std. Mean Difference | Risk of Bias |
|-------------------|--------------|---------|----------------------|----------------------|--------------|
|                   | Mean SD Total | Mean SD Total | IV Fixed 95% CI     | IV Fixed 95% CI     | A B C D E F G |
| 1.2.1 C v.s. placebo | 110.7 87.1 181.7 | 108.38 34 9.7% | -0.72 [-1.20, -0.23] |                   |
| Hashemzadeh et al. 2020 | 14.53 7.18 36 | 21.23 7.11 35 9.4% | -0.93 [-1.42, -0.44] |                   |
| Haryan et al. 2018 | 6.1 1.9 19 9.4 | 3.4 21 5.2% | -1.02 [-1.58, -0.46] |                   |
| Total (95% CI) | 157 | 158 43.7% | -0.66 [-0.88, -0.43] |                   |
| Heterogeneity: | \( \chi^2 = 4.58, df = 3 \) (P = 0.21); I² = 34% | Test for overall effect: Z = 5.64 (P < 0.0001) |

| 1.2.2 C v.s. NSAIDs | 3.25 2.11 171 | 3.17 1.96 160 48.9% | 0.04 [-0.18, 0.25] |                   |
| Total (95% CI) | 171 | 160 48.9% | 0.04 [-0.18, 0.25] |                   |
| Heterogeneity: Not applicable | Test for overall effect: Z = 0.35 (P = 0.72) |

| 1.2.3 C+NSAIDs v.s. NSAIDs | 9.48 0.17 78 | 10.16 0.16 82 7.5% | -4.10 [-4.65, -3.55] |                   |
| Total (95% CI) | 78 | 82 7.5% | -4.10 [-4.65, -3.55] |                   |
| Heterogeneity: Not applicable | Test for overall effect: Z = 14.60 (P < 0.0001) |

| Risk of bias legend | favourite if experimental favourite if control |
|---------------------|------------------|
| A Random sequence generation (selection bias) | |
| B Allocation concealment (selection bias) | |
| C Blinding of participants and personnel (performance bias) | |
| D Blinding of outcome assessment (detection bias) | |
| E Incomplete outcome data (attrition bias) | |
| FSelective reporting (reporting bias) | |
| G Other biases | |

Figure 5 WOMAC score-pain

### 3.4.2 Function

The improvement of function is represented by the results of WOMAC score-function. 6 RCTs reported WOMAC score-function of patients [16-18, 20, 33-34, 38-39]. These RCTs are divided into different subgroups according to their intervention group and control group: (1) Curcuma longa Extract and curcumin (C.) v.s. placebo; (2) C. v.s. NSAIDs; (3) C.+NSAIDs v.s. NSAIDs. The heterogeneity
test showed that the heterogeneity of the main subgroups was high \([(1): I^2 = 75\%, P=0.008; (2)-(3): \text{not applicable}]$, so the random effects model was used for meta-analysis. The meta-analysis results of each subgroup showed that: (1) Compared with placebo, Curcuma longa Extract and curcumin can reduce WOMAC score-function (SMD -0.79, 95%CI -1.27 to -0.31, P=0.001; random effect model). (2) Compared with the NSAIDs group, there was no statistical difference in the improvement of WOMAC score-function by Curcuma longa Extract and curcumin (SMD 0.07, 95%CI -0.14 to 0.29, P=0.51; random effect model); (3) Compared with the NSAIDs group, the WOMAC score-function in C.+NSAIDs group was lower (SMD -3.81, 95%CI -4.34 to -3.29, P<0.00001; random effect model). The summary result also showed the WOMAC score-function in experimental group was lower (SMD -1.17, 95%CI -2.20 to -0.14, P=0.03; random effect model). (Figure 6).

| Study or Subgroup | Experimental Mean | SD | Control Mean | SD | Total Weight | Std. Mean Difference | Risk of Bias |
|------------------|-------------------|----|--------------|----|--------------|----------------------|--------------|
| Wang et al. 2020 | 398.4 491.61 | 676.6 325.16 | 34 16.6% | -0.75 [-1.24, -0.26] | A |
| Hashemzadeh et al. 2020 | 42.61 16.7 | 69.51 27.56 | 35 16.6% | -1.17 [-1.66, -0.67] | B |
| Hanoy et al. 2018 | 4.37 9.02 | 12.76 66 | 17.0% | -0.25 [-0.59, 0.09] | C |
| Panahi et al. 2014 | 15.7 10.34 | 20 15.4 | 23 18.1% | -1.17 [-1.94, -0.40] | D |
| Subtotal (95% CI) | 157 | 158 15.6% | 66.3% | -0.97 [-1.27, -0.31] | E |

Figure 6 WOMAC score-function

### 3.4.3 Stiffness

The improvement of function is represented by the results of WOMAC score-stiffness. 6 RCTs reported WOMAC score-stiffness of patients \([16-18, 20, 33-34, 38-39]\). These RCTs are divided into different subgroups according to their intervention group and control group: (1) Curcuma longa Extract and curcumin (C.) v.s. placebo; (2) C. v.s. NSAIDs; (3) C.+ NSAIDs v.s. NSAIDs. The heterogeneity test showed that the heterogeneity of the main subgroups was low \([(1): I^2 = 25\%, P=0.25; (2)-(3): not applicable]$. The summary result also showed the WOMAC score-function in experimental group was lower (SMD -1.17, 95%CI -2.20 to -0.14, P=0.03; random effect model). (Figure 6).

Risk of bias legend:
- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other biases
applicable], so the fix effects model was used for meta-analysis. The meta-analysis results of each subgroup showed that: (1) Compared with placebo, Curcuma longa Extract and curcumin can reduce WOMAC score-stiffness (SMD -0.35, 95%CI -0.57 to -0.12, P=0.002; fix effect model). (2) Compared with the NSAIDs group, there was no statistical difference in the improvement of WOMAC score-stiffness by Curcuma longa Extract and curcumin (SMD 0.05, 95%CI -0.17 to 0.27, P=0.65; fix effect model); (3) Compared with the NSAIDs group, the WOMAC score-stiffness in C.+NSAIDs group was lower (SMD -0.45, 95%CI -0.77 to -0.14, P=0.005; fix effect model). The summary result also showed the WOMAC score-stiffness in experimental group was lower (SMD -0.20, 95%CI -0.34 to -0.06, P=0.004; fix effect model). (Figure 7).

3.5 Secondary outcomes

The results of KOOS score and MDA were shown in Table 2. Only Panahi et al. 2016 [30] reported the improvement of SOD and GSH. This RCT found that compared with placebo, the serum SOD activities in curcuminoids group was higher (P<0.001). However, the difference of GSH level between curcuminoids group and placebo group was of no statistical significance (P=0.064).

Only Kertia et al. 2012 [32] reported the improvement of COX-2. This RCT found that the difference in COX-2 between diclofenac sodium group and curcuminoid group was of no statistical
significance (P=0.89).

Table 2: The secondary outcomes

| Secondary outcomes | Overall effect | Heterogeneity test | Figure | Reference |
|--------------------|---------------|-------------------|--------|-----------|
|                    | MD 95%CI      | P Tau² I² P       |        |           |
| KOOS- Function in daily living | -3.27 [-3.27,-0.06] | 0.04 0 0.94 | fix effect | 2 264 | Fig S1 [18, 20] |
| KOOS- Function in sport and recreation | -4.26 [-4.26,-0.71] | 0.06 0 0.49 | fix effect | 2 264 | Fig S2 [18, 20] |
| Quality of life | -7.48,3.56 | 0.49 12.91 | random | 2 264 | Fig S3 [18, 20] |
| MDA | -3.80 [-3.80,-0.32] | 0.02 1.49 | <0.0001 | random | 2 213 | Fig S4 [30, 39] |

3.6 Adverse events

Ten (10) RCTs [16-20, 31, 33-36, 38-39] reported adverse events. These RCTs are divided into different subgroups according to their intervention group and control group: (1) Curcuma longa Extract and curcumin (C.) v.s. placebo; (2) C. v.s. NSAIDs; (3) C.+ NSAIDs v.s. NSAIDs; (4) C. +Glucosamine v.s. Glucosamine. The heterogeneity test showed that the heterogeneity of the subgroups was high [(1): I²=25%, P=0.25; (2): I²= 70%, P=0.03; (3)-(4): not applicable], so the random effects model was used for meta-analysis. The meta-analysis results of each subgroup showed that: (1) The difference of incidence of adverse events between Curcuma longa Extract and curcumin group and placebo group was of no statistical significance (RR 1.18, 95%CI 0.71 to 1.94, P=0.52; random effect model). (2) Compared with the NSAIDs group, the incidence of adverse events in
Curcuma longa Extract and curcumin was lower (RR 0.55, 95%CI 0.34 to 0.88, P=0.01; random effect model); (3) Compared with the NSAIDs group, the incidence of adverse events in C.+NSAIDs group did not increase (RR 0.53, 95%CI 0.10 to 2.79, P=0.45; random effect model); (4) The difference of adverse events between Glucosamine group and C.+ Glucosamine group was of no statistical significance (RR 0.80, 95%CI 0.24 to 2.69, P=0.72; random effect model). The summary result also showed the adverse events between in experimental group and control group was of no statistical significance (RR 0.77, 95%CI 0.56 to 1.05, P=0.10; random effect model). (Figure 8).

3.7 Publication Bias Detection

The publication bias of the primary outcomes were detected by STATA 15.0. (1) VAS: The
publication bias detection suggests that there may be no publication bias ($P=0.125$) (Figure 9A). (2) WOMAC score-pain: The publication bias detection suggests that there may be no publication bias ($P=0.301$) (Figure 9B). (3) WOMAC score-function: The publication bias detection suggests that there may be no publication bias ($P=0.565$) (Figure 9C). (4) WOMAC score-stiffness: The publication bias detection suggests that there may be no publication bias ($P=0.138$) (Figure 9D). (5) Adverse events: The publication bias detection suggests that there may be no publication bias ($P=0.372$) (Figure 9E).

Figure 9 The results of publication bias detection (A: VAS; B: WOMAC score-pain; C: WOMAC score-function; D: WOMAC score-stiffness; E: Adverse events).
score-function; D: WOMAC score-stiffness; E: adverse events)

## 3.8 Impact of Time of treatment

In order to explore the influence of the duration of the intervention on the primary outcomes, we conducted a subgroup analysis of the main results according to the duration of the intervention (Table 3). (1) Pain: VAS showed a difference in the fourth week after the intervention, but there was no difference in the sixth week, and the results after 12 weeks showed a difference again. WOMAC-pain showed different results, there was no difference in the fourth week, and after the sixth week, the results of the two groups showed a difference. (2) WOMAC-function: WOMAC-function showed a difference in the 6th week, but there was no difference between the two groups in the 12th week. (3) WOMAC-stiffness: The result of WOMAC-stiffness in the 6th week was marginal (P=0.05), and the difference began to appear in the 12th week. (4) Adverse events: There was a difference in the results at the 6th week, but there was no difference in the results at other time points.

### Table 3 Impact of Time of treatment

| Duration of treatment | Outcome | Overall effect | 95% CI | P   | Tau² | I² (%) | P   | Statistic method | Studies (N) | Sample size (N) | Heterogeneity test | Figure |
|-----------------------|---------|----------------|--------|-----|------|--------|-----|------------------|-------------|------------------|-------------------|--------|
| 4 weeks VAS           | -6.33   | -              |        | 0.02| 26.43| 94     | <0.000| Rando m          | 4            | 352              | S5                |        |
| 4 weeks WOMA          | -0.02   | [-0.21, 0.82]  | 0.29   | 10  | Not  | Not    | Not | Fixed            | 1            | 331              | S6                |        |
| 4 weeks C-pain        | 0.16    | [0.14, 0.51]   | 0.29   |     |      |        |      |                  |              |                  | Not applicable    |        |
| 4 weeks C-function    | 0.29    | [0.24, 0.65]   | 0.29   | 80  | 0.02 | Rando  | 2    | 470              |              |                  | Fig               |        |

Note: The table above shows the impact of time on various outcome measures. For each measure, the table lists the duration, the overall effect size, the 95% confidence interval, p-value, and other statistical details. The figures referenced (S5, S6, S7, S8) likely correspond to graphs or additional tables that are not included in the text but can be found in the supplementary materials or the full report.
| Events | VAS   | WOMA C-pain | WOMA C-function | WOMA C-stiffness | Adverse events |
|--------|-------|-------------|-----------------|------------------|----------------|
| 6      | -6.26 | -0.96       | -1.17           | -0.37            | 0.56           |
| 8      | -11.47| -0.5         | -0.47           | -0.33            | 1.38           |
| 16     | -1.08 | -0.33       | -0.47           | -0.33            | 1.38           |

**Weeks**

| Events | VAS   | WOMA C-pain | WOMA C-function | WOMA C-stiffness | Adverse events |
|--------|-------|-------------|-----------------|------------------|----------------|
| 6      | -15.91| -1.35       | -1.57           | -0.75            | 0.38           |
| 12     | -11.47| -0.78       | -0.78           | -0.61            | 0.68           |
| 16     | -1.12 | -0.61       | -0.61           | -0.61            | 0.68           |
4 Discussion

For a long time, plant-derived drugs have been highly valued by researchers in the treatment of arthritis. Curcuma, the main active ingredient of Curcuma longa Extract, is a representative plant-derived medicine. Compared with NSAIDs, it has obvious anti-inflammatory and antioxidant effects and no adverse reactions such as gastrointestinal tract, which indicates that it may become a substitute for NSAIDs [40-41]. A large number of pharmacological studies have also revealed that curcumin has the potential to become a clinical treatment for OA [41-43]. For example, curcumin inhibits inflammation by blocking inflammatory factor-mediated NF-κB, NLRP3 and other signaling pathways, and inhibits oxidation by removing free radicals and enhancing antioxidant enzyme activity, thereby protecting cartilage from damage [44-46]. Curcumin can also promote cartilage matrix repair by adjusting the levels of proteins such as synthin, inhibit chondrocyte apoptosis by promoting autophagy and increasing the activity of anti-apoptotic proteins, and affect chondrocyte proliferation by regulating the Wnt signaling pathway [41-43].

In this systematic review and meta-analysis, we found that: (1) compared with placebo, Curcuma longa Extract and curcumin can relieve pain (decrease the VAS and WOMAC score-pain), improve
the joint function (decrease the WOMAC score-function), and improve the joint stiffness (decrease the WOMAC score-stiffness); in terms of adverse events, Curcuma longa Extract and curcumin are comparable to those of placebo, suggesting that Curcuma longa Extract and curcumin are safe. (2) Compared with NSAIDs, Curcuma longa Extract and curcumin have similar effects on joint pain, function and stiffness. However, the incidence of adverse events in Curcuma longa Extract and curcumin was lower. (3) Compared with the NSAIDs group, Curcuma longa Extract and curcumin+NSAIDs can also relieve pain (decrease the VAS and WOMAC score-pain), improve the joint function (decrease the WOMAC score-function), and improve the joint stiffness (decrease the WOMAC score-stiffness); in terms of adverse events, the addition of Curcuma longa Extract and curcumin to NSAIDs did not increase adverse events; However, due to the small number of RCTs, no definite conclusion can be drawn. (4) The difference of VAS and incident of adverse events between Glucosamine group and C.+ Glucosamine group was of no statistical significance. (5) Compared with control group, KOOS-function in daily living, KOOS- Function in sport and recreation, MDA level in Curcuma longa Extract and curcumin group is lower. (6) For other oxidative stress indicators (SOD, GSH) and COX-2, since RCTs are less, no definite conclusion can be drawn. (7) In the 12th week of the intervention, Pain, function, and stiffness all showed improvement, suggesting that 12 weeks may be an important time point. (8) The heterogeneous of some outcomes are high (such as, adverse events, MDA, VAS, etc.). These heterogeneity may be related to the difference in preparation and dosage. According to the subgroup analysis based on the duration of the intervention, although the pain, function, and stiffness were inconsistent at the time point before 12 weeks, they all showed improvement after 12 weeks. This suggests that the administration of Curcuma longa Extract and curcumin must last at least 12 weeks to allow different groups to achieve therapeutic effects. The differences in the results of various indicators at different time points may be related to differences in regions, races, pharmaceutical preparations, drug dosages and so on. Adverse events decreased in the 6th week, and there was no significant difference compared with the control group at other time points. This may indicate that the 6-week intervention is the time point with the least adverse events, or it may be caused by differences in race, administration methods, and pharmaceutical preparations. In the future, it is still necessary to report more outcomes data at different time points of Curcuma longa Extract and curcumin's intervention to correct or confirm this result. Current research reports also show that curcumin can inhibit the inflammatory response upstream phospholipase A2 (phospholipase A2,
PLA2), COX-2, 5-lipoxygenase (5-lipoxygenase, 5-LOX), iNOS activity. This in turn inhibits the production of inflammatory factors such as midstream IL1β, IL-6, IL-8, TNF-α, and further inhibits the degradation of cartilage matrix by downstream MMP-3, MMP-9 [47-49]. Curcumin can also increase antioxidant enzyme activity and regulate oxidative stress by regulating signal pathways such as Nrf2-ARE, NFκB, MAPK, Notch, AMPK) and NADPH/ROS [50-51].

In addition, we can pay more attention to the role of Curcuma longa in OA in the future. Curcuma longa contains more phenolic pigments (including curcumin, demethoxycurcumin, bisdemethoxycurcumin) and essential oils (including cineole, linalool, α-terpinene, caryophyllene, ar-curcumene, zingiberen, curcumol, dl-turmerone, artumerone, dehydrocurdione); it also contains campesterol, stigmasterol, β-sitosterol, cholesterol, fatty acids and metal elements potassium, sodium, magnesium, calcium, manganese, iron, copper, zinc and other multi-component botanicals [52-55]. Compared with curcumin monomer, because Curcuma longa extract contains more components, it may play a multi-target and multi-signal pathway transduction role in the treatment of OA pain and inflammation in the molecular pathology mechanism [56-57]. Meanwhile, Curcuma longa is a multi-component botanical drug, and the synergy between its components may bring potential clinical effects in the treatment of OA [58-59]. These components may increase the concentration of each other in the blood of patients with OA through pharmacokinetics and increase the time of each other's stay in the body, thereby exerting a better clinical effect. Current research showed that the bioavailability of curcumin compound monomers is low [60-61]. However, through the combination with piperine and other substances, the blood concentration of curcumin increased, the elimination half-life was prolonged, the metabolic clearance rate was reduced, and the bioavailability was improved [62-64]. Curcuma longa is a multi-component botanical drug, and the synergy between its different components may also reduce potential side effects. Recent studies have shown that Curcuma longa is generally well tolerated even in large doses, although there are still some gastrointestinal side effects, such as nausea and diarrhea, and allergic reactions [65]. Recent studies have also shown the clinical efficacy of Curcuma longa extract in OA [16, 18]. In the future, the synergistic relationship between the multiple components of Curcuma longa can be further explored.

To promote the conclusion, the GRADE tool was utilized to rate the quality of the evidence [66]. According to the GRADE handbook [53], the evidence was judged to be high to moderate (Table 4). The quality of WOMAC score-pain and WOMAC score-stiffness was high; the quality of VAS,
WOMAC score-function, adverse events was moderate (Table 4).

Table 4 Summary of findings for the main comparison

| Patient or population: patients with OA |
|----------------------------------------|

| Outcomes               | Illustrative comparative risks* (95% CI) | Relative effect (95% CI) | No of Participants (studies) | Quality of the evidence (GRADE) | Comments |
|------------------------|------------------------------------------|--------------------------|-----------------------------|---------------------------------|----------|
| **Primary outcomes**   |                                          |                          |                             |                                 |          |
| VAS                    | The mean vas in the intervention groups was 6.23 lower (10.15 to 2.31 lower) | 823 (10 studies)         | ⊕⊕⊕                        | moderate                       |          |
| WOMAC score-pain       | The mean womac pain in the intervention groups was 0.57 standard deviations lower (0.73 to 0.42 lower) | 806 (6 studies)          | ⊕⊕⊕                       | high                           | SMD -0.57 (-0.73 to -0.42) |
| WOMAC score-function   | The mean womac function in the intervention groups was 1.17 standard deviations lower (2.2 to 0.14 lower) | 806 (6 studies)          | ⊕⊕⊕                        | moderate                       | SMD -1.17 (-2.2 to -0.14)  |
| WOMAC score-stiffness  | The mean womac stiffness in the intervention groups was 0.2 standard deviations lower (0.34 to 0.06 lower) | 806 (6 studies)          | ⊕⊕⊕                        | high                           | SMD -0.2 (-0.34 to -0.06)  |
| Adverse events         | Study population RR 0.77 (0.56 to 1.05) (14 studies) | 1410 (14 studies)        | ⊕⊕⊕                        | moderate                       |          |
|                       | 246 per 1000                             | 189 per 1000 (138 to 258) | Moderate                    |                                 |          |
|                       | 133 per 1000                             | 102 per 1000 (74 to 140)  |                             |                                 |          |

*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio;

GRADE Working Group grades of evidence

**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

1 Downgraded one level due to the probably substantial heterogeneity

Some of our results agree with the meta-analysis of Bannuru et al. For example, we have found that Curcuma longa Extract and curcumin can improve pain, function and stiffness compared with placebo. We also found that there is no difference between Curcuma longa Extract and NSAIDs in improving pain, function and stiffness. In terms of adverse events, we all found that Curcuma longa Extract is as safe as placebo and safer than NSAIDs. However, our study included the RCT of Curcuma longa Extract and curcumin combined with NSAIDs, and showed that this combination is more effective than NSAIDs alone, and the addition of Curcumin does not increase the occurrence of adverse events. Our study also evaluated the effects of Curcuma longa Extract and curcumin in combination with Glucosamine, and found that the pain improvement and the incidence of adverse events in the Curcuma longa Extract and curcumin+Glucosamine group were similar to those in the Glucosamine group. However, because there are too few RCTs related to Curcuma longa Extract and curcumin+Glucosamine and Curcuma longa Extract and curcumin+NSAIDs, it is not enough to draw a very positive conclusion. In the future, more related RCTs are needed to verify or modify this results. Our meta-analysis also showed that Curcuma longa Extract and curcumin can improve oxidative stress in patients with OA. Compared with previous meta-analysis, our risk of bias assessment results are different, but we list the reasons for the assessment in detail. And our GRADE score shows that the level of evidence is higher, possibly because our assessment of the risk of bias is lower, and the heterogeneity of RCTs is lower. Our meta-analysis also shows that Curcuma longa Extract and curcumin may need to be administered for at least 12 weeks to obtain the therapeutic effect. In addition, the RCTs we included are more novel, which increases the reliability of the conclusions. Our meta-analysis shows that the combination of Curcumin and NSAIDs does not increase the occurrence of adverse events and has better efficacy. This is a promising result, because adding Curcumin supplementation in the case of using NSAIDs may increase the efficacy and perhaps reduce the dosage of NSAIDs. This is a direction that can be studied in the future.

In view of the broad prospects of the current development and application of curcumin or
Curcuma longa Extract in the treatment of OA, it is recommended that future RCT research can be in-depth from the following aspects: (1) Explore the effects of different administration routes of Curcuma longa Extract and curcumin (such as oral, topical percutaneous application, joint cavity injection, etc.) on its curative effect, and find the best administration method, concentration and dosage of curcumin in the treatment of OA. (2) The role of Curcuma longa Extract and curcumin combined with other active ingredients (such as quercetin, etc.) in the treatment of OA. (3) Report outcomes at different intervention time points. In addition, due to the difference in the incidence of OA between male and female [68], we look forward to future RCTs to analyze the efficacy and safety of different genders, so as to provide more detailed guidance on the medication of patients of different genders.

5 Conclusion

This systematic review and meta-analysis show that Curcuma longa Extract and curcumin can relieve pain and joint stiffness in patients with OA, improve joint function, and would not increase the occurrence of adverse events. Based on current evidence, it is recommended to use Curcuma longa Extract and curcumin supplement for OA patients for more than 12 weeks. Future RCTs can focus on the different usage and dosage of Curcuma longa Extract and curcumin, and the curative effect of combination with other drugs.

Data Availability Statement

The data that support the findings of this study are openly available in supplementary materials.

Conflict of Interest

We declare no competing interests.

Author contributions

Liuting Zeng, Ganpeng Yu, Hua Chen are responsible for the study concept and design. Liuting Zeng, Kailin Yang, Wensa Hao, Ganpeng Yu, Hua Chen are responsible for the data collection, data analysis and interpretation; Liuting Zeng and Kailin Yang drafted the paper; Hua Chen and Ganpeng Yu supervised the study; all authors participated in the analysis and interpretation of data and approved the final paper.

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| Study or Subgroup | Experimental | Control | Std. Mean Difference | Risk of Bias |
|------------------|-------------|---------|----------------------|--------------|
|                  | Mean        | SD      | Total                | IV, Random, 95% CI | IV, Random, 95% CI | A | B | C | D | E | F | G |
| 3.1 C v.s. placebo | 398.4       | 401.61  | 36 676.6 325.16      | 34 16.6% -0.75 [-1.24, -0.26] | 34 16.6% -1.17 [-1.68, -0.67] |
| Wang et al. 2020 | 42.61       | 16.7    | 36 69.51 27.56       | 35 16.6% -1.17 [-1.68, -0.67] | 35 16.6% -0.75 [-1.24, -0.26] |
| Hashemzadeh et al. 2020 | 4.37 9.02 66 7.16 12.76 68 17.0% -0.25 [-0.59, 0.09] | 68 17.0% -0.25 [-0.59, 0.09] |
| Panahi et al. 2014 | 18.7 10.3 19 30.4 9.4 21 16.1% -1.17 [-1.84, -0.49] | 21 16.1% -1.17 [-1.84, -0.49] |
| Subtotal (95% CI) | 157         | 158     | 66.3% -0.79 [-1.27, -0.31] | -0.79 [-1.27, -0.31] |
| Heterogeneity: Tau² = 0.18; Chi² = 11.79, df = 3 (P = 0.008); I² = 75% |
| Test for overall effect: Z = 3.24 (P = 0.001) |

3.2 C v.s. NSAIDs

| Study or Subgroup | Experimental | Control | Std. Mean Difference | Risk of Bias |
|------------------|-------------|---------|----------------------|--------------|
| Kupirmiratskul et al. 2014 | 3.41 2.09 171 3.26 2.05 160 17.2% 0.07 [-0.14, 0.29] | 160 17.2% 0.07 [-0.14, 0.29] |
| Subtotal (95% CI) | 171         | 160     | 17.2% 0.07 [-0.14, 0.29] |
| Heterogeneity: Not applicable|
| Test for overall effect: Z = 0.66 (P = 0.51) |

3.3 C+NSAID v.s. NSAIDs

| Study or Subgroup | Experimental | Control | Std. Mean Difference | Risk of Bias |
|------------------|-------------|---------|----------------------|--------------|
| Srivastava et al. 2016 | 32.14 0.4 78 33.88 0.5 82 16.5% -3.81 [-4.34, -3.29] | 82 16.5% -3.81 [-4.34, -3.29] |
| Subtotal (95% CI) | 78          | 82      | 16.5% -3.81 [-4.34, -3.29] |
| Heterogeneity: Not applicable|
| Test for overall effect: Z = 14.25 (P < 0.00001) |

| Total (95% CI) | 406       | 400     | 100.0% -1.17 [-2.28, -0.14] | -1.17 [-2.28, -0.14] |
| Heterogeneity: Tau² = 1.59; Chi² = 193.34, df = 5 (P < 0.00001); I² = 97% |
| Test for overall effect: Z = 2.23 (P = 0.03) |
| Test for subgroup differences: Chi² = 181.70, df = 2 (P < 0.00001), I² = 98.9% |

Risk of bias legend:
- A: Random sequence generation (selection bias)
- B: Allocation concealment (selection bias)
- C: Blinding of participants and personnel (performance bias)
- D: Blinding of outcome assessment (detection bias)
- E: Incomplete outcome data (attrition bias)
- F: Selective reporting (reporting bias)
- G: Other biases
Records identified through Chinese databases searching (n = 135):
- CNKI (21) - Wan Fang (70)
- VIP (20) - CBM (24)

Records identified through other language databases searching (n = 544):
- PubMed (122) - EMBASE (202)
- The Cochrane Library (69)
- Web of Science (126)
- Medline Complete (14)
- ClinicalTrials.gov (11)

Records after duplicates removed (n = 679)

Records screened (n = 679)

Records excluded based on the title and abstract: (n = 656)

Full-text articles assessed for eligibility (n = 22)

Full-text articles excluded, with reasons (n = 7)

Studies included in qualitative synthesis (n = 15)

Studies included in quantitative synthesis (meta-analysis) (n = 15)
| Study                          | Random sequence generation (selection bias) | Allocation concealment (selection bias) | Blinding of participants and personnel (performance bias) | Blinding of outcome assessment (detection bias) | Incomplete outcome data (attrition bias) | Selective reporting (reporting bias) | Other biases |
|-------------------------------|---------------------------------------------|----------------------------------------|----------------------------------------------------------|--------------------------------------------------|----------------------------------------|--------------------------------------|--------------|
| Wang et al. 2020              | +                                           | +                                     | +                                                        | +                                                | +                                     | +                                    | +            |
| Srivastava et al. 2016        | +                                           | +                                     | +                                                        | +                                                | +                                     | +                                    | +            |
| Shep et al. 2019              | +                                           | +                                     | +                                                        | +                                                | +                                     | +                                    | +            |
| Pinsonnak et al. 2012         | +                                           | +                                     | +                                                        | +                                                | +                                     | +                                    | +            |
| Panahi et al. 2014            | +                                           | +                                     | +                                                        | +                                                | +                                     | +                                    | +            |
| Nakagawa et al. 2014          | +                                           | +                                     | +                                                        | +                                                | +                                     | +                                    | +            |
| Madhu et al. 2013             | +                                           | +                                     | +                                                        | +                                                | +                                     | +                                    | +            |
| Kuplniraiakul et al. 2009     | +                                           | +                                     | +                                                        | +                                                | +                                     | +                                    | +            |
| Keria et al. 2012             | +                                           | +                                     | +                                                        | +                                                | +                                     | +                                    | +            |
| Jamali et al. 2020            | +                                           | +                                     | +                                                        | +                                                | +                                     | +                                    | +            |
| Herrein et al. 2020           | +                                           | +                                     | +                                                        | +                                                | +                                     | +                                    | +            |
| Haroyan et al. 2018           | +                                           | +                                     | +                                                        | +                                                | +                                     | +                                    | +            |
| Study or Subgroup | Experimental | Control | Mean Difference | Mean Difference | Risk of Bias |
|------------------|--------------|---------|----------------|----------------|--------------|
|                  | Mean SD     | Total   | IV Random 95% CI | IV Random 95% CI | A B C D E F G |
| C v. placebo     | 31.2 19.26  | 36     | 28.49          | 34             | 6.2% -8.60 [-20.06, 2.86] |
| Jamali et al. 2020 | 45.2 17.8   | 36     | 16.5           | 36             | 8.6% -11.40 [-19.33, -3.47] |
| Henrotin et al. 2019a | 38 4 | 49 49 | 1          | 23 13.2% -11.00 [-12.19, -9.81] |
| Henrotin et al. 2019b | 37 4 | 47 49 | 1          | 22 13.2% -12.00 [-13.22, -10.78] |
| Panahi et al. 2014 | 36 18 | 19 35 | 15          | 21 6.9% 1.00 [-9.33, 11.33] |
| Madhu et al. 2013a | 19.48 17.94 | 29 46.03 | 20.84          | 29 7.2% -26.55 [-36.53, -16.57] |
| Total (95% CI)   | 216 165    | 55.4% -11.55 [-14.93, -8.96] |
| Heterogeneity: Tau² = 3.78; Chi² = 15.93, df = 5 (P = 0.007); I² = 69% |
| Test for overall effect: Z = 9.11 (P < 0.00001) |

1.2 C v. NSAIDs

Shep et al. 2019 | 22 8.1 | 70 22 6.1 | 69 12.8% | 0.00 [-2.38, 2.38] |
Kumpinratasekul et al. 2009 | 2.7 2.5 | 45 3.1 | 2.3 46 13.3% | -0.40 [-1.39, 0.59] |
Subtotal (95% CI) | 115 115 | 26.0% -0.34 [-1.25, 0.57] |
| Heterogeneity: Tau² = 0.00; Chi² = 0.09, df = 1 (P = 0.76); I² = 0% |
| Test for overall effect: Z = 0.73 (P = 0.46) |

1.3 C+NSAIDs v. NSAIDs

Srivastava et al. 2016 | 4.03 0.08 | 78 5.11 | 0.14 82 13.4% | -1.08 [-1.12, -1.04] |
| Subtotal (95% CI) | 78 82 | 13.4% -1.08 [-1.12, -1.04] |
| Heterogeneity: Not applicable |
| Test for overall effect: Z = 60.27 (P < 0.00001) |

1.4 C+Glucosamine v. Glucosamine

Madhu et al. 2013b | 36.33 28.99 | 28 29.29 | 20.58 24 5.2% | 7.04 [6.49, 20.57] |
| Subtotal (95% CI) | 28 24 | 5.2% 7.04 [6.49, 20.57] |
| Heterogeneity: Not applicable |
| Test for overall effect: Z = 1.02 (P = 0.31) |

Total (95% CI) | 437 386 | 100.0% -6.23 [-10.15, -2.31] |
| Heterogeneity: Tau² = 29.90; Chi² = 611.38, df = 9 (P < 0.00001); I² = 99% |
| Test for overall effect: Z = 3.11 (P = 0.002) |
| Test for subgroup differences: Chi² = 72.04, df = 3 (P < 0.00001), I² = 95.8% |

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other biases
### 2.2.1 C vs. placebo

| Study or Subgroup       | Experimental Mean | SD | Total | Control Mean | SD | Total | Weight | Std. Mean Difference IV, Fixed, 95% CI | Risk of Bias |
|-------------------------|-------------------|----|-------|--------------|----|-------|--------|--------------------------------------|--------------|
| Wang et al. 2020        | 110.7             | 87.1| 36     | 181.7        | 108.38| 34     | 9.7%   | -0.72 [-1.20, -0.23]                  | C C C C C C  |
| Hashemzadeh et al. 2020 | 14.53             | 7.18| 36     | 21.23        | 7.11 | 35     | 9.4%   | -0.93 [-1.42, -0.44]                  | C C C C C C  |
| Haroyan et al. 2018     | 4.05              | 3.1 | 66     | 5.16         | 2.42 | 68     | 19.4%  | -0.40 [-0.74, -0.06]                  | C C C C C C  |
| Panahi et al. 2014      | 6.1               | 2.9 | 19     | 9.4          | 3.4  | 21     | 5.2%   | -1.02 [-1.66, -0.36]                  | C C C C C C  |
| Subtotal (95% CI)       | 157               |    | 158    |              |     | 43.7%  |        | -0.66 [-0.88, -0.43]                  |                          |

- Heterogeneity: Chi² = 4.58, df = 3 (P = 0.21); I² = 34%
- Test for overall effect: Z = 5.64 (P < 0.00001)

### 2.2.2 C vs. NSAIDs

| Study or Subgroup       | Experimental Mean | SD | Total | Control Mean | SD | Total | Weight | Std. Mean Difference IV, Fixed, 95% CI | Risk of Bias |
|-------------------------|-------------------|----|-------|--------------|----|-------|--------|--------------------------------------|--------------|
| Kuprinatsaikul et al. 2014 | 3.25             | 2.11| 171    | 3.17        | 1.98 | 160    | 48.9%  | 0.04 [-0.18, 0.25]                    | C C C C C C  |
| Subtotal (95% CI)       | 171               |    | 160    |              |     | 48.9%  |        | 0.04 [-0.18, 0.25]                    |                          |

- Heterogeneity: Not applicable
- Test for overall effect: Z = 0.35 (P = 0.72)

### 2.2.3 C+NSAIDs vs. NSAIDs

| Study or Subgroup       | Experimental Mean | SD | Total | Control Mean | SD | Total | Weight | Std. Mean Difference IV, Fixed, 95% CI | Risk of Bias |
|-------------------------|-------------------|----|-------|--------------|----|-------|--------|--------------------------------------|--------------|
| Srivastava et al. 2016  | 9.48              | 0.17| 78     | 10.16       | 0.16 | 82     | 7.5%   | -4.10 [-4.65, -3.55]                  | C C C C C C  |
| Subtotal (95% CI)       | 78                |    | 82     |              |     | 7.5%   |        | -4.10 [-4.65, -3.55]                  |                          |

- Heterogeneity: Not applicable
- Test for overall effect: Z = 14.60 (P < 0.00001)

### Total

| Study or Subgroup       | Experimental Mean | SD | Total | Control Mean | SD | Total | Weight | Std. Mean Difference IV, Fixed, 95% CI | Risk of Bias |
|-------------------------|-------------------|----|-------|--------------|----|-------|--------|--------------------------------------|--------------|
| Total                   | 406               |    | 400    |              |     | 100.0%|        | -0.57 [-0.73, -0.42]                  |                          |

- Heterogeneity: Chi² = 193.86, df = 5 (P < 0.000001); I² = 97%
- Test for overall effect: Z = 7.47 (P < 0.00001)
- Test for subgroup differences: Chi² = 189.28, df = 2 (P < 0.000001), I² = 98.9%

### Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other biases
### Study or Subgroup

| Study or Subgroup | Experimental Mean | SD | Total | Control Mean | SD | Total | Std. Mean Difference IV. Fixed, 95% CI | Std. Mean Difference IV. Fixed, 95% CI | Risk of Bias |
|-------------------|------------------|----|-------|--------------|----|-------|-------------------------------------|-------------------------------------|-------------|
| 4.4.4 4 Weeks     |                  |    |       |              |    |       |                                     |                                     |             |
| Kuptnisai-kul et al. 2014 | 3.28            | 2.38| 171   | 3.16         | 2.36| 160   | 41.6%                               | 0.05 [-0.17, 0.27]                   |             |
| Subtotal (95% CI) | 171              |    |       | 160          |    |       | 41.6%                               | 0.05 [-0.17, 0.27]                   |             |
| Heterogeneity: Not applicable |                  |    |       |              |    |       |                                     |                                     |             |
| Test for overall effect: Z = 0.46 (P = 0.65) |                  |    |       |              |    |       |                                     |                                     |             |
| 4.4.5 6 Weeks     |                  |    |       |              |    |       |                                     |                                     |             |
| Hashemzadeh et al. 2020 | 2.64            | 1.93| 36    | 2.94         | 2.04| 35    | 8.9%                                | -0.15 [-0.62, 0.32]                  |             |
| Panahi et al. 2014 | 0.15            | 0.5 | 19    | 0.76         | 0.9 | 21    | 4.6%                                | -0.81 [-1.46, -0.16]                 |             |
| Subtotal (95% CI) | 55               |    |       | 56           |    |       | 13.5%                               | -0.37 [-0.75, 0.00]                  |             |
| Heterogeneity: Chi² = 2.63, df = 1 (P = 0.10); I² = 62% |                  |    |       |              |    |       |                                     |                                     |             |
| Test for overall effect: Z = 1.94 (P = 0.05) |                  |    |       |              |    |       |                                     |                                     |             |
| 4.4.6 12 Weeks    |                  |    |       |              |    |       |                                     |                                     |             |
| Wang et al. 2020   | 48.6            | 42.14| 36   | 76.2         | 53.64| 34    | 8.4%                                | -0.57 [-1.05, -0.09]                 |             |
| Haroyan et al. 2018 | 1.58            | 1.7 | 66    | 1.95         | 1.76| 68    | 16.8%                               | -0.21 [-0.55, 0.13]                  |             |
| Subtotal (95% CI) | 102              |    |       | 102          |    |       | 25.2%                               | -0.33 [-0.61, -0.05]                 |             |
| Heterogeneity: Chi² = 1.41, df = 1 (P = 0.24); I² = 29% |                  |    |       |              |    |       |                                     |                                     |             |
| Test for overall effect: Z = 2.35 (P = 0.02) |                  |    |       |              |    |       |                                     |                                     |             |
| 4.4.7 16 Weeks    |                  |    |       |              |    |       |                                     |                                     |             |
| Srivastava et al. 2016 | 4.06            | 0.17| 78   | 4.16         | 0.18| 82    | 19.6%                               | -0.45 [-0.77, -0.14]                 |             |
| Subtotal (95% CI) | 78               |    |       | 82           |    |       | 19.6%                               | -0.45 [-0.77, -0.14]                 |             |
| Heterogeneity: Not applicable |                  |    |       |              |    |       |                                     |                                     |             |
| Test for overall effect: Z = 2.84 (P = 0.005) |                  |    |       |              |    |       |                                     |                                     |             |
| 406 total          |                  |    |       | 400          |    |       | 100.0%                              | -0.20 [-0.34, -0.06]                 |             |
| Heterogeneity: Chi² = 13.43, df = 5 (P = 0.02); I² = 63% |                  |    |       |              |    |       |                                     |                                     |             |
| Test for overall effect: Z = 2.85 (P = 0.004) |                  |    |       |              |    |       |                                     |                                     |             |
| Test for subgroup differences: Chi² = 9.39, df = 3 (P = 0.02), I² = 68.1% |                  |    |       |              |    |       |                                     |                                     |             |

**Risk of bias legend**

- **A** Random sequence generation (selection bias)
- **B** Allocation concealment (selection bias)
- **C** Blinding of participants and personnel (performance bias)
- **D** Blinding of outcome assessment (detection bias)
- **E** Incomplete outcome data (attrition bias)
- **F** Selective reporting (reporting bias)
- **G** Other biases

**Favours [experimental]**

**Favours [control]**

- **10**
- **5**
- **0**
- **-5**
- **-10**

![Graph showing the results of the study comparisons](image-url)
### 4.7.1 4 Weeks

| Study or Subgroup | Experimental Events | Control Events | Total Events | Total Weight | Risk Ratio M-H Random, 95% CI | Risk Ratio M-H Random, 95% CI | Risk of Bias |
|-------------------|---------------------|----------------|--------------|--------------|-------------------------------|-------------------------------|--------------|
| Shep et al. 2019  | 9                   | 70             | 26           | 69           | 0.34 [0.17, 0.67]             |                               | A B C D E F G |
| Kuptniratsakul et al. 2014 | 55                 | 171            | 65           | 160          | 0.79 [0.59, 1.06]             |                               | A B C D E F G |
| Subtotal (95% CI) | 241                 | 229            | 33.4%        |             | 0.55 [0.24, 1.26]             |                               | A B C D E F G |
| Total events      | 64                  | 91             |              |              |                               |                               | A B C D E F G |
| Heterogeneity: Tau\(^2\) = 0.29; Chi\(^2\) = 5.10, df = 1 (P = 0.02); I\(^2\) = 80% |
| Test for overall effect: Z = 1.41 (P = 0.16) |

### 4.7.2 6 Weeks

| Study or Subgroup | Experimental Events | Control Events | Total Events | Total Weight | Risk Ratio M-H Random, 95% CI | Risk Ratio M-H Random, 95% CI | Risk of Bias |
|-------------------|---------------------|----------------|--------------|--------------|-------------------------------|-------------------------------|--------------|
| Jamali et al. 2020 | 0                   | 36             | 0            | 36           | Not estimable                 |                               | A B C D E F G |
| Hashemzadeh et al. 2020 | 0                 | 36             | 0            | 35           | Not estimable                 |                               | A B C D E F G |
| Kuptniratsakul et al. 2009 | 16               | 45             | 33           | 46           | 17.6% 0.50 [0.32, 0.76]       |                               | A B C D E F G |
| Panahi et al. 2014  | 3                   | 19             | 4            | 21           | 4.6% 0.83 [0.21, 3.24]        |                               | A B C D E F G |
| Madhu et al. 2013a  | 2                   | 30             | 2            | 30           | 2.6% 1.00 [0.15, 6.64]        |                               | A B C D E F G |
| Madhu et al. 2013b  | 4                   | 30             | 5            | 30           | 5.5% 0.80 [0.24, 2.69]        |                               | A B C D E F G |
| Subtotal (95% CI) | 196                 | 198            | 30.2%        |             | 0.56 [0.38, 0.82]             |                               | A B C D E F G |
| Total events      | 25                  | 44             |              |              |                               |                               | A B C D E F G |
| Heterogeneity: Tau\(^2\) = 0.00; Chi\(^2\) = 1.37, df = 3 (P = 0.71); I\(^2\) = 0% |
| Test for overall effect: Z = 3.00 (P = 0.003) |

### 4.7.3 8 Weeks

| Study or Subgroup | Experimental Events | Control Events | Total Events | Total Weight | Risk Ratio M-H Random, 95% CI | Risk Ratio M-H Random, 95% CI | Risk of Bias |
|-------------------|---------------------|----------------|--------------|--------------|-------------------------------|-------------------------------|--------------|
| Nakagawa et al. 2014 | 0                   | 18             | 0            | 23           | Not estimable                 |                               | A B C D E F G |
| Subtotal (95% CI) | 18                  | 23             |              |              |                               |                               | A B C D E F G |
| Total events      | 0                   | 0              |              |              |                               |                               | A B C D E F G |
| Heterogeneity: Not applicable |
| Test for overall effect: Not applicable |

### 4.7.4 12 Weeks

| Study or Subgroup | Experimental Events | Control Events | Total Events | Total Weight | Risk Ratio M-H Random, 95% CI | Risk Ratio M-H Random, 95% CI | Risk of Bias |
|-------------------|---------------------|----------------|--------------|--------------|-------------------------------|-------------------------------|--------------|
| Henrotin et al. 2019a | 18                  | 49             | 3            | 23           | 6.2% 2.82 [0.92, 8.61]        |                               | A B C D E F G |
| Henrotin et al. 2019b | 10                  | 47             | 3            | 22           | 5.7% 1.56 [0.48, 5.11]        |                               | A B C D E F G |
| Haroyan et al. 2016 | 7                   | 66             | 4            | 68           | 5.7% 1.80 [0.55, 5.87]        |                               | A B C D E F G |
| Wang et al. 2020    | 14                  | 36             | 18           | 34           | 15.5% 0.73 [0.44, 1.23]       |                               | A B C D E F G |
| Subtotal (95% CI)  | 198                 | 147            | 33.1%        |             | 1.38 [0.68, 2.81]             |                               | A B C D E F G |
| Total events       | 49                  | 28             |              |              |                               |                               | A B C D E F G |
| Heterogeneity: Tau\(^2\) = 0.28; Chi\(^2\) = 6.64, df = 3 (P = 0.06); I\(^2\) = 55% |
| Test for overall effect: Z = 0.88 (P = 0.38) |

### 4.7.5 16 Weeks

| Study or Subgroup | Experimental Events | Control Events | Total Events | Total Weight | Risk Ratio M-H Random, 95% CI | Risk Ratio M-H Random, 95% CI | Risk of Bias |
|-------------------|---------------------|----------------|--------------|--------------|-------------------------------|-------------------------------|--------------|
| Srivastava et al. 2016 | 2                   | 78             | 4            | 82           | 3.2% 0.53 [0.10, 2.79]        |                               | A B C D E F G |
| Subtotal (95% CI) | 78                  | 82             | 3.2%         |             | 0.53 [0.10, 2.79]             |                               | A B C D E F G |
| Total events      | 2                   | 4              |              |              |                               |                               | A B C D E F G |
| Heterogeneity: Not applicable |
| Test for overall effect: Z = 0.76 (P = 0.45) |

### 4.7.6 Total

| Study or Subgroup | Experimental Events | Control Events | Total Events | Total Weight | Risk Ratio M-H Random, 95% CI | Risk Ratio M-H Random, 95% CI | Risk of Bias |
|-------------------|---------------------|----------------|--------------|--------------|-------------------------------|-------------------------------|--------------|
| Total (95% CI)    | 731                 | 679            | 100.0%       |             | 0.77 [0.56, 1.05]             |                               | A B C D E F G |
| Total events      | 140                 | 167            |              |              |                               |                               | A B C D E F G |
| Heterogeneity: Tau\(^2\) = 0.10; Chi\(^2\) = 18.03, df = 10 (P = 0.05); I\(^2\) = 45% |
| Test for overall effect: Z = 1.64 (P = 0.10) |
| Test for subgroup differences: Chi\(^2\) = 5.11, df = 3 (P = 0.16), I\(^2\) = 41.3% |

**Risk of bias legend**

1. Random sequence generation (selection bias)
2. Allocation concealment (selection bias)
3. Blinding of participants and personnel (performance bias)
4. Blinding of outcome assessment (detection bias)
5. Incomplete outcome data (attrition bias)
6. Selective reporting (reporting bias)
7. Other biases
# PRISMA 2009 Checklist

| Section/topic | # | Checklist item                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Reported on page # |
|---------------|---|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|
| TITLE         |   | **TITLE**                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                   |
|               |   | Title 1 Identify the report as a systematic review, meta-analysis, or both.                                                                                                                                                                                                                                                                                                                                     | 1                 |
| ABSTRACT      |   | **ABSTRACT**                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 1-2               |
|               |   | Structured summary 2 Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.                                                                                                                                                                                              |                   |
| INTRODUCTION  |   | **INTRODUCTION**                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 2-3               |
|               |   | Rationale 3 Describe the rationale for the review in the context of what is already known.                                                                                                                                                                                                                                                                                                                      |                   |
|               |   | Objectives 4 Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).                                                                                                                                                                                                                                          | 2-3               |
| METHODS       |   | **METHODS**                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 3-5               |
|               |   | Protocol and registration 5 Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.                                                                                                                                                                                                                                            |                   |
|               |   | Eligibility criteria 6 Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.                                                                                                                                                                                                                                           | 3-5               |
|               |   | Information sources 7 Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.                                                                                                                                                                                                                               | 3-5               |
|               |   | Search 8 Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.                                                                                                                                                                                                                                                                              | 3-5               |
|               |   | Study selection 9 State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).                                                                                                                                                                                                                                             | 3-5               |
|               |   | Data collection process 10 Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.                                                                                                                                                                                                                           | 3-5               |
|               |   | Data items 11 List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.                                                                                                                                                                                                                                                                      | 3-5               |
|               |   | Risk of bias in individual studies 12 Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.                                                                                                                                                                           | 3-5               |
|               |   | Summary measures 13 State the principal summary measures (e.g., risk ratio, difference in means).                                                                                                                                                                                                                                                                                                                 | 3-5               |
|               |   | Synthesis of results 14 Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.                                                                                                                                                                                                                                               | 3-5               |
## PRISMA 2009 Checklist

| Section/topic                        | #  | Checklist item                                                                                           | Reported on page # |
|--------------------------------------|----|-----------------------------------------------------------------------------------------------------------|--------------------|
| Risk of bias across studies          | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | 3-5                |
| Additional analyses                  | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | -                  |
| **RESULTS**                          |    |                                                                                                           |                    |
| Study selection                      | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | 5-20               |
| Study characteristics                | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | 5-20               |
| Risk of bias within studies          | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | 5-20               |
| Results of individual studies        | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | 5-20               |
| Synthesis of results                 | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | 5-20               |
| Risk of bias across studies          | 22 | Present results of any assessment of risk of bias across studies (see Item 15).                             | 5-20               |
| Additional analysis                  | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | -                  |
| **DISCUSSION**                      |    |                                                                                                           |                    |
| Summary of evidence                  | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | 20-24              |
| Limitations                          | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | 20-24              |
| Conclusions                          | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | 24                 |
| **FUNDING**                          |    |                                                                                                           |                    |
| Funding                              | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | 24                 |

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.
Table S1. Search Strategies for PubMed and Embase

| PubMed                                                                 | Embase                                                                 |
|-----------------------------------------------------------------------|-----------------------------------------------------------------------|
| (Curcumin OR Curcumas OR Tumeric OR Tumerics OR Turmeric OR Turmerics OR Curcuma zedoaria OR Curcuma zedoarias OR zedoaria, Curcuma OR Zedoary zedoaria OR Zedoary zedoarias OR zedoaria, Zedoary OR Curcuma longa OR Curcuma longas OR longa, Curcuma OR Curcuma Longa) AND | 1 'Curcumin' OR 'Curcumas' |
| (Osteoarthritis OR Osteoarthritides OR Osteoarthrosis OR Osteohrothres OR Arthritis, Degenerative OR Arthritises, Degenerative OR Degenerative Arthritis OR Osteoarthrosis Deformans) AND | 2 'Tumeric' OR 'Tumerics' OR 'Turmeric' OR 'Turmerics' |
| (random* controlled trial [pt] OR controlled clinical trial* [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR random* [tiab] OR trial* [tiab] OR group* [tiab]) NOT | 3 'Zedoary zedoaria' OR 'Zedoary zedoarias Curcuma longa' |
| (animals [mh] NOT humans [mh])                                        | 4 'Curcuma zedoaria' OR 'Curcuma zedoarias' OR 'Curcuma longas' OR 'Curcuma Longa' |
|                                                                       | 5 1 or 2 or 3 or 4                                                    |
|                                                                       | 6 'Osteoarthritis/exp'                                                |
|                                                                       | 7 'Osteoarthritides' or 'Osteoarthrosis' or 'Osteoarthroses'          |
|                                                                       | 8 'Degenerative Arthritis' OR 'Degenerative Arthritis' OR 'Osteoarthrosis Deformans' |
|                                                                       | 9 6 or 7 or 8                                                         |
|                                                                       | 10 5 and 9                                                           |
|                                                                       | 11 'randomized controlled trial'                                      |
|                                                                       | 12 'single blind procedure' or 'double blind procedure'               |
|                                                                       | 13 'crossover procedure'                                              |
|                                                                       | 14 12 or 13 or 14                                                     |
|                                                                       | 15 10 and 14                                                          |
| Study or Subgroup | Mean | SD  | Total | Mean | SD  | Total | Weight | IV, Fixed, 95% CI | Mean Difference | IV, Fixed, 95% CI | Risk of Bias |
|-------------------|------|-----|-------|------|-----|-------|--------|-------------------|----------------|-------------------|-------------|
| Henrotin et al. 2019a | 40.6 | 20.78 | 47 | 41.6 | 10.85 | 20 | 4.4% | -1.00 [-8.61, 6.61] | -0.46 [-8.37, 7.45] | -0.39 [-8.50, 7.72] | **G** |
| Henrotin et al. 2019b | 38.6 | 23.22 | 38 | 41.6 | 10.85 | 20 | 3.3% | -3.00 [-11.78, 5.78] | -0.32 [-8.11, 7.47] | -0.94 [-8.37, 6.51] | **E G** |
| Jep et al. 2019 | 94.58 | 6.58 | 70 | 96.23 | 2.71 | 69 | 92.2% | -1.65 [-3.32, 0.02] | -0.34 [-0.67, 0.00] | -0.25 [-0.57, 0.07] | **D G** |

Total (95% CI) 155 109 100.0% -1.67 [-3.27, -0.06]
| Risk of Bias | Study or Subgroup | Mean Weight (g) | SD | Total Mean Weight (g) | IV Fixed, 95% CI |
|-------------|------------------|----------------|----|-----------------------|-----------------|
|             |                  |                |    |                       |                 |
| A           |                  | 154.7          | 36.8|                      |                 |
| B           |                  | 174.7          | 43  |                      |                 |
| C           |                  | 187            | 47  |                      |                 |
| D           |                  | 198.7          | 70  |                      |                 |
| E           |                  | 198.7          | 98  |                      |                 |

# Risk of Bias Legend

A. Random sequence generation (selection bias)
B. Allocation concealment (selection bias)
C. Blinding of participants and personnel (performance bias)
D. Blinding of outcome assessment (detection bias)
E. Incomplete outcome data (attrition bias)
F. Selective reporting (reporting bias)
G. Other biases

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**Test for overall effect:** Z = 2.74 (P = 0.006)
### Study or Subgroup

| Study or Subgroup       | Mean | SD  | Total | Mean | SD  | Total | Weight | IV, Random, 95% CI | Mean Difference | IV, Random, 95% CI | Risk of Bias |
|-------------------------|------|-----|-------|------|-----|-------|--------|-------------------|-----------------|-------------------|--------------|
| Panahi et al. 2016      | 17   | 2   | 27    | 20   | 1   | 26    | 47.1%  | -3.00 [-3.85, -2.15] | -3.00 [-3.85, -2.15] |                  | 4 ? ? ? ? ? ? ? ? |
| Srivastava et al. 2016  | 3.69 | 0.12| 78    | 4.91 | 0.11| 82    | 52.9%  | -1.22 [-1.26, -1.18] | -1.22 [-1.26, -1.18] |                  | 4 ? ? ? ? ? ? ? ? |

### Total (95% CI)

- Heterogeneity: Tau² = 1.49; Chi² = 16.95, df = 1 (P < 0.0001); I² = 94%
- Test for overall effect: Z = 2.32 (P = 0.02)

The plot shows that the mean difference is favoring the control group. The risk of bias is depicted by the legend:

- A: Random sequence generation (selection bias)
- B: Allocation concealment (selection bias)
- C: Blinding of participants and personnel (performance bias)
- D: Blinding of outcome assessment (detection bias)
- E: Incomplete outcome data (attrition bias)
- F: Selective reporting (reporting bias)
- G: Other biases
### Table 1: Summary of Study Results

| Subgroup | Experimental | Control | Mean Difference | Std. Mean Difference | SD | Total Mean | SD | Total Weight | IV Random | 95% CI |
|----------|--------------|---------|-----------------|---------------------|----|------------|----|-------------|-----------|--------|
| 12 Weeks | 406.44       | 388.4   | 18.04           | 2.92                | 0.4| 76         | 33.8| 70          | 1.91      | 0.97   |
| 16 Weeks | 406.44       | 388.4   | 18.04           | 2.92                | 0.4| 76         | 33.8| 70          | 1.91      | 0.97   |

#### Risk of Bias

- **A:** Random sequence generation (selection bias)
- **B:** Allocation concealment (selection bias)
- **C:** Blinding of participants and personnel (performance bias)
- **D:** Blinding of outcome assessment (detection bias)
- **E:** Incomplete outcome data (attrition bias)
- **F:** Selective reporting (reporting bias)
- **G:** Other bias

#### Notes

- Total (95% CI) = 406.44 - 388.4 = 18.04 (95% CI = 2.92 ± 0.4, df = 70, P < 0.00001)
- Test for overall effect: Z = 2.92 (df = 70, P < 0.00001)
- Test for subgroup differences: CH² = 18.44, df = 3 (P < 0.00001), I² = 96.4%