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Original Article

Efficacy of *Curcuma longa* in relieving pain symptoms of knee osteoarthritis patients: a systematic review and meta-analysis of clinical trials

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Objective: Osteoarthritis (OA), particularly knee OA, affects 24% of adults and is a significant cause of disability. Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used but have many adverse effects. Antioxidant and anti-iflammatory properties of *Curcuma longa* might decrease pain thus improving joint function.

Methods: This systematic review and meta-analysis evaluated randomized controlled trials (RCTs) on *Curcuma longa* efficacy for knee OA. We reported mean differences (MD) with 95% confidence interval (CI) for continuous outcomes and evaluated Visual Analog Scale (VAS) for pain and the Western Ontario and McMaster Universities Arthritis Index (WOMAC) total score over 4 to 6 weeks for treatment effects.

Results: Ten RCTs with 786 patients were included. *Curcuma longa* significantly improved VAS for pain than placebo (MD: 18.25, 95% CI: 7.79 to 28.72, p=0.0006). It was not inferior to NSAIDs in WOMAC total score improvement (MD: −11.99, 95% CI: −39.21 to 15.23, p=0.39). Both dosages (<1,000 and ≥1,000 mg/day) of *Curcuma longa* demonstrated similar improvement in VAS for pain compared to placebo (MD: 27.02, 95% CI: 1.45 to 52.60, p=0.04; MD: 21.48, 95% CI: 1.78 to 41.18, p=0.03).

Conclusion: *Curcuma longa* benefits knee OA pain and function, being more effective than placebo and comparable to NSAIDs. Despite positive results, limitation and heterogeneity of the studies necessitates further research to explore optimal dosages and administration methods of *Curcuma longa* as therapeutic option for knee OA.

Keywords: Knee osteoarthritis, *Curcuma*, Visual Analog Scale, Western Ontario and McMaster Universities Arthritis Index

INTRODUCTION

Osteoarthritis (OA) is the most common arthritis, resulting in disability in 24% of the general adult population. OA is characterized by bone remodelling, cartilage degradation, osteophyte formation, and synovial inflammation. These processes lead to symptoms of joint pain, swelling, stiffness, and consequently, loss of normal joint function found in OA patients [1-3]. OA is believed to be caused by biomechanical and inflammatory processes related to injury, age, oxidative and mechanical stress,

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obesity, and metabolic disease. Chemical mediators found in synovial fluid were believed to support inflammation and catabolism, resulting in cartilage degeneration of OA [4].

Chronic inflammation accompanied by joint pain and dysfunction occurring in OA requires its patients to receive long-term management [5]. Currently, the management of OA is addressed to alleviate pain, slow the progression of degeneration, and improve or restore joint function beneficial to the patients. Recommended treatments for OA are usually categories into three: pharmacological, non-pharmacological, and surgical interventions selected according to disease stages [6]. Pharmacological intervention remains the most prevalent option, using nonsteroidal anti-inflammatory drugs (NSAIDs) like ibuprofen, naproxen, salicylates, selective cyclooxygenase-2 (COX-2) inhibitor, chondroitin sulphate, glucosamine, capsaicin, hyaluronic acid, and steroids. However, long-term use of these medications is associated with cardiovascular, renal, gastrointestinal, lung, liver, skin, and central nervous system adverse events [7]. Therefore, concerns about the safety profiles of current therapy have led researchers to explore alternatives investigating the use of natural remedies that are considered safer [8].

Several herbs were evaluated and used for the treatment of OA, including *Curcuma longa* and god's crown (*Phaleria macrocarpa*) extract [7]. *Curcuma longa*, commonly known as Turmeric, is a herbaceous perennial plant which belongs to the *Zingiberaceae* (ginger) family. It has been extensively used as spices in food as well as in folk medicine [9,10]. The major constituent of *Curcuma longa,* namely Curcumin, a polyphenol, is believed to be potentially therapeutic in various diseases [11,12]. It is accessible in many forms including tablets, capsules, ointments, drinks, and cosmetics [12]. Chinese use this plant as medications to relieve sore throat, urticaria, dermatitis, hepatitis, as well as inflammatory joints [13]. It is also one of oldest spices in India and is believed by communities to have biological actions as Kustaghna (anti-dermatosis), Visaghna (anti-poisonous), and Dashemani Lekhaniya (emaciating) [14]. The use of Curcumin in medication has solidly inhibited the making of pro-inflammation mediators, including tumor necrosis factor-alpha (TNF-α), nitric oxide synthase (NOS), interleukin 1 (IL-1), and interleukin 8. Furthermore, Curcumin also inhibits COX-2, suppressing the synthesis of prostaglandin. Curcumin was clinically beneficial in the improvement of Visual Analog Scale (VAS) and the Western Ontario and McMaster Universities Arthritis Index (WOMAC score based on the latest clinical studies. With the gradual increase in number of studies and the accumulation of findings, it is important to update the findings of latest clinical trials and analyse the effect of *Curcuma longa* for knee OA patients [5].

MATERIALS AND METHODS

Design

We reported our meta-analysis according to the Cochrane Handbook of Systematic Reviews of Interventions and followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statements. This systematic review was registered in the PROSPERO (CRD42023464474) prior to submission.

Search strategy

The search of potential studies was conducted using electronic databases of Scopus, PubMed, Embase, Cochrane Library, and Google Scholar from September 2013 to September 2023. We focused on randomized controlled trials (RCTs) that evaluated efficacy of *Curcuma longa* extract for knee OA patients. Electronic searches were performed using keywords (osteoarthritis [MeSH Heading term]) OR (osteoarthritis, knee [MeSH Heading term]) OR (knee osteoarthritis) AND (curcuma longa supplementation) OR (curcuma longa supplement) OR (curcumin [MeSH Heading term]) OR (turmeric) OR (curcuminoid) AND (placebo) OR (anti-inflammatory agents [MeSH Heading term]) AND (disease activity) OR (clinical improvement) OR (Visual Analog Scale [MeSH Heading term]) OR (Western Ontario and McMaster Universities Arthritis Index) to search articles from databases as described in the Supplementary Table 1 (Search Strategy). The application of similar strategies were executed on other databases.

Study selection criteria

Three reviewers performed the initial search independently, removed duplications, and screened the titles and abstracts considered relevant. In the event of uncertainty, we determined eligibility according to full-text review and discussions to resolve any issue of study selections.

The following criteria were used for study inclusion (Supplementary Table 2) : (a) population (P): patients diagnosed with knee OA (b) intervention (I): oral administration of *Curcuma longa* extract, Curcumin, or active compound of *Curcuma*; (c)

comparison (C): oral administration of placebo or pain relievers; and (d) one of more of the following outcomes (O): visual analogue scale for pain (VAS for pain) and WOMAC score. Our searches were limited to studies involving humans and only those written in English.

Non-RCT studies, studies in a language other than English, patients who have knee trauma or injury history or have undergone surgery for knee OA, using topical *Curcuma longa* extract, treatment using *Curcuma longa* in combination with other herbal compounds, and insufficent data were excluded from this meta-analysis.

Data extraction

Three independent reviewers extracted data by screening titles and abstracts in Rayyan software (Rayyan, Cambridge, MA, USA) for systematic review. Selected studies were screened for full-text build upon the selection criteria. Studies selected for review were determined by majority agreement. Data extraction was executed according to the following data: study design, study population, and outcome measures.

Risk of Bias assessment

We used the Cochrane Risk of Bias tool of the Cochrane manual (Version 5.0.1, The Cochrane Collaboration) in determining the evidence certainty for each outcome accounted essential of the included RCTs. The tool assesses randomization, intervention deviations, outcome data, measurement of outcome, and selection of reported result. Regarding discrepancies, a resolution was made through reviewers' discussion until a consensus was reached. The risk bias mapping of included studies was produced using Review Manager Web (The Cochrane Collaboration).

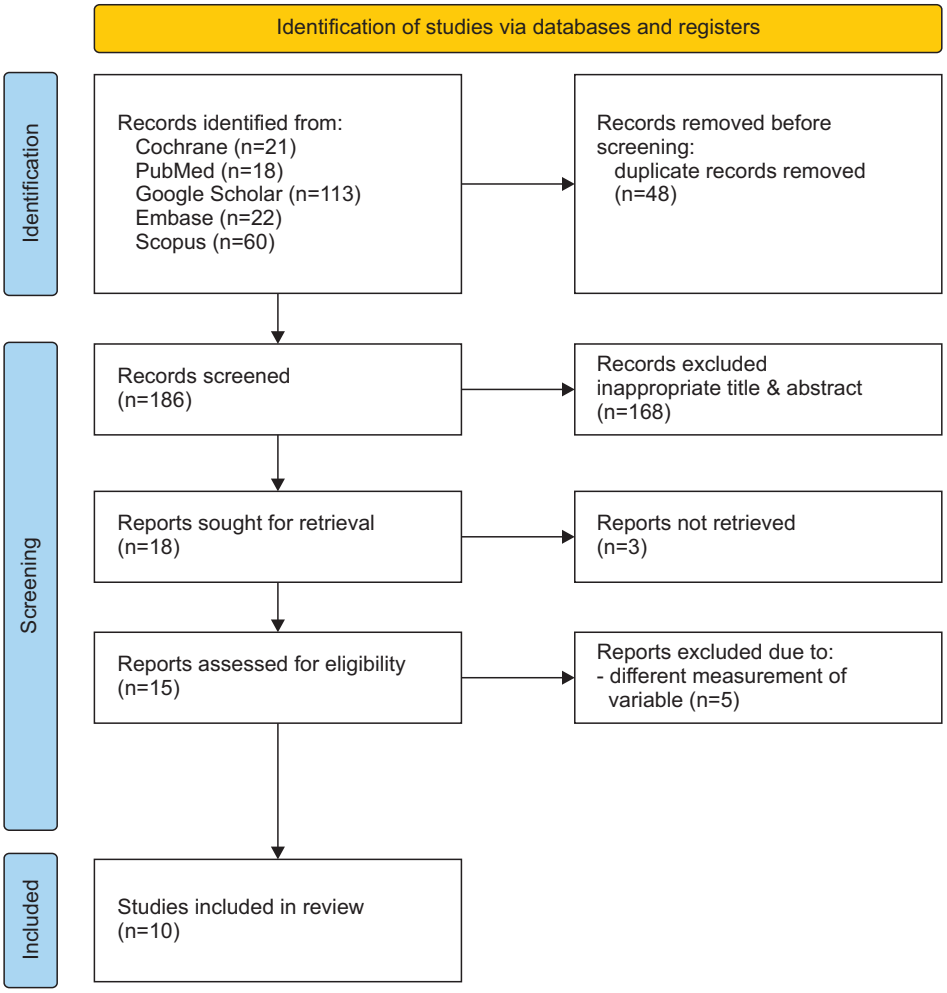

Figure 1. Flowchart of identification and screening process for eligible randomized controlled trials.

Table 1. Characteristics of included studies

Study	Country	Number of patients		Female/male		Mean age (yr)		Target-population	Diagnostic-criteria	K-Lgrade	Inter-vention	Comparator	Treatment duration	Study design	Outcome
		CL	Placebo/control	CL	Placebo/control	CL	Placebo/control								
Wang et al. [38]	Australia	35	32	18/18	21/13	61.3	62.4	Knee OA patients	ACR	NR	500 mg CL, BID	Placebo, BID	12 wks	RCT, DB	VAS for pain, MRI, WOMAC pain, function, and stiffness scores, cartilage composition values, and adverse events
Panahi et al. [18]	Iran	19	21	22/5	22/4	57.3	57.6	Knee OA patients	ACR	2-3	500 mg CL, BID	Placebo, TID	6 wks	RCT, DB	VAS for pain, WOMAC pain, function, stiffness, and total scores, Lequesne's pain functional index, and adverse events
Srivastava et al. [17]	India	78	82	53/25	50/32	50.2	50.3	Knee OA patients	ACR	1-4	500 mg CL, BID	Placebo, BID	16 wks	RCT	VAS for pain, WOMAC pain, function, and stiffness scores, laboratory tests, and adverse events
Nakagawa et al. [19]	Japan	15	20	21/4	20/5	71.9	66.1	Knee OA patients	Radiological evidence	2-3	540 mg CL, BID	Placebo, BID	8 wks	RCT	VAS for pain, Japanese knee osteoarthritis measure, and NSAID consumption
Henrotin et al. [22]	Belgium	52	46	40/9	34/13	61.4	63.3	Knee OA patients	ACR	2-4	93 mg CL, BID	Placebo, BID	12 wks	RCT, DB	VAS for pain, KOOS score, laboratory tests, NSAID consumption, adverse events, and patient's satisfaction

Table 1. Continued

Study	Country	Number of patients		Female/male		Mean age (yr)		Target-population	Diagnostic-criteria	K-Lgrade	Inter-vention	Comparator	Treatment duration	Study design	Outcome
		CL	Placebo/control	CL	Placebo/control	CL	Placebo/control								
Madhu et al. [20]	India	29	29	17/13	17/13	56.6	56.8	Knee OA patients	Clinical evidence	2-3	500 mg CL, BID	Placebo, BID	6 wks	RCT	VAS for pain, Japanese knee osteoarthritis measure, and NSAID consumption
Atabaki et al. [21]	Iran	15	15	15/0	15/0	49.1	48.3	Knee OA patients	ACR	2-3	80 mg CL, QID	Placebo, QID	12 wks	RCT, DB	VAS for pain and laboratory tests
Gomes et al. [5]	Brazil	8	7	1/7	0/7	64.5	59.0	Knee OA patients	ACR	1-3	500 mg CL, BID	600 mg Ibuprofen, BID	30 d	RCT	WOMAC pain, function, stiffness, VAS for pain and laboratory tests
Singhal et al. [23]	India	73	71	20/53	17/54	53.1	50.8	Knee OA patients	ACR	2-4	500 mg CL, BID	650 mg Paracetamol, TID	6 wks	RCT	WOMAC pain and adverse events
Shep et al. [24]	India	70	69	45/25	48/21	53.1	52.1	Knee OA patients	ACR	NR	500 mg CL, TID	50 mg Natrium diclofenac, BID	4 wks	RCT	VAS for pain, KOOS subscale, anti-flatulent and weight-lowering activity, global assessment by physicians and patients, adverse reactions, and laboratory tests result

BID: twice per day, CL: *Curcuma longa* extract, DB: double blind, KOOS: Knee Injury and Osteoarthritis Outcome Score, MRI: magnetic resonance imaging, NSAID: nonsteroidal anti-inflammatory drugs, OA: osteoarthritis, QID: four times a day, RCT: randomized controlled trial, TID: three times a day, VAS: Visual Analog Scale, WOMAC: Western Ontario and McMaster Universities Arthritis Index, ACR: American College of Rheumatology, K-L: Kellgren and Lawrence grading scale, NR: not reported.

Statistical analysis

We used the Review Manager Web for data analysis and synthesis, as well as for generating forest plots. Continuous outcomes were reported as mean differences (MD) with 95% confidence interval (CI) using different scales. Meta-analysis used the random effects model to anticipate variation between studies.

The treatment effect were calculated from the difference between the pre-intervention and post-intervention changes of the outcome measures VAS for pain and WOMAC total score, performed within 4 to 6 weeks or a month duration treatment of control groups. WOMAC total scores were divided into two groups comparing the use of *Curcuma longa* vs. placebo and *Curcuma longa* vs. NSAIDs. We performed a subgroup analysis for the placebo-controlled group to explore further impact on different daily dosages of *Curcuma longa* (dose <1,000, or dose ≥1,000 mg/day). The subgroup analysis was only performed on VAS for pain due to limited data for the WOMAC total score. In assessing heterogeneity across studies, we used the I^2 statistic with 25, 50, and 75% values indicating low, moderate, and high heterogeneity [15]. In addition, the 95% CIs for I^2 were also calculated [16]. Funnel plots were used in investigating bias secondary to small study effects. All analyses were conducted using Review Manager Web. The results of two-sided p-values <0.05 were considered statistically significant.

RESULTS

We were able to identify 234 records in the initial search. After removing duplicate records, 186 studies remained for reading titles and abstracts. After screening for titles and abstracts, 18 studies remained for full-text reading. We then excluded three studies due to full-text unavailability. Fifteen RCTs remained for further evaluation and after eligibility assessment five studies were excluded due to different variable measurements. Finally, 10 studies were included in this study. The PRISMA flowchart of the identification and screening process for eligible studies is shown in Figure 1.

This study included 10 RCTs from six countries in sum. A

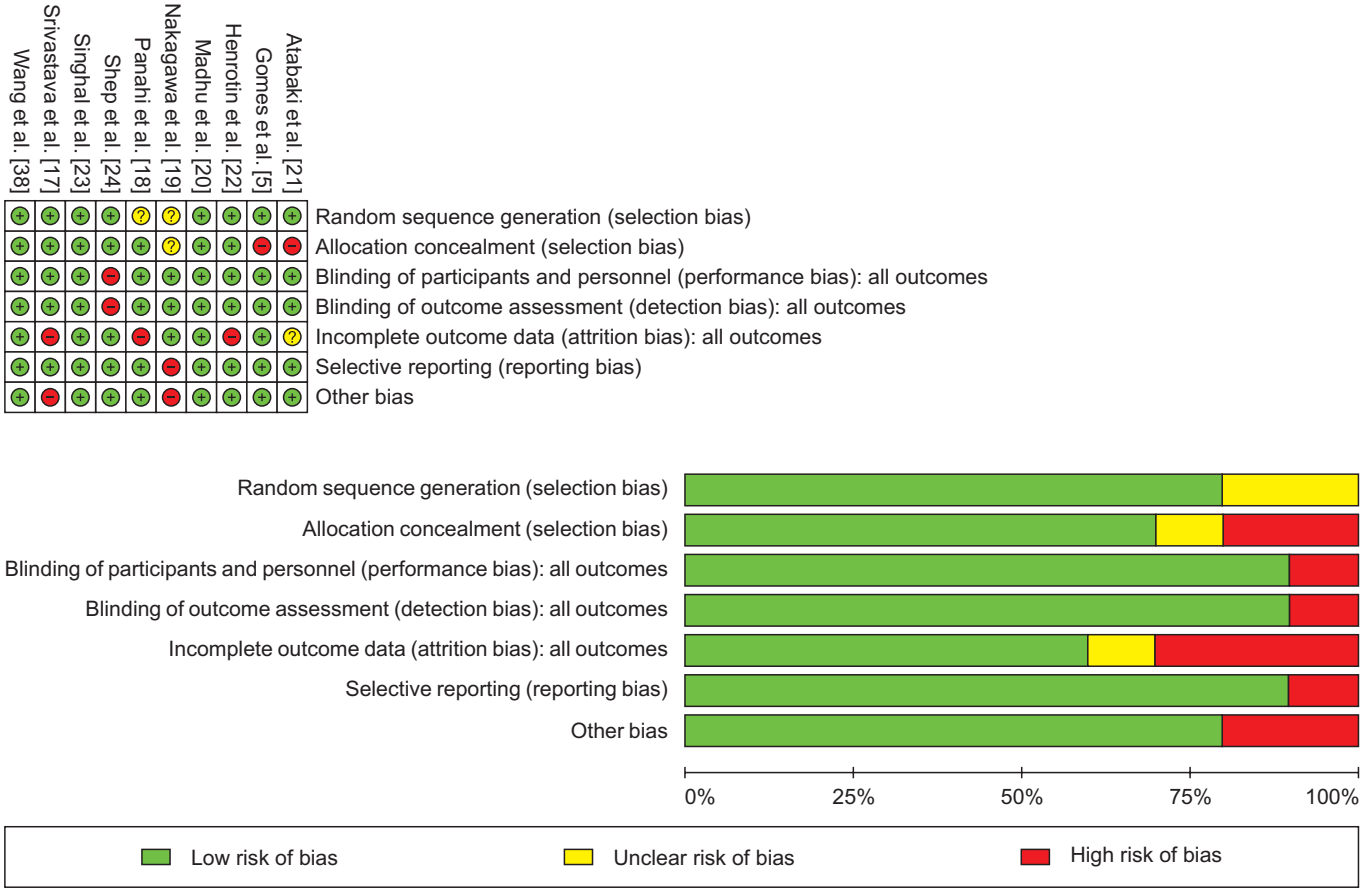

Figure 2. Detailed risk of bias among included randomized controlled trials.

total of 786 knee OA patients were included in this study, comprising 394 in the *Curcuma longa* extract group and 392 in the placebo group, with the sample size of the studies ranging from 7 to 82. The most commonly used diagnostic criteria in 8 out of 10 studies included were the ACR criteria. The OA severity was classified according to the Kellgren and Lawrence grading scale (K-L) in 8 out of 10 studies included [5,17-23], with one study [5] of patients with a K-L grade 1 to 3, one study [17] of patients with K-L grade 1 to 4, four studies [17-21] with a K-L grade 2 to 3, and two studies [22,23] with K-L grade from 2 to 4 before treatment. This study involves three types of interventions: Curcumin, NSAIDs, and placebo. The treatment duration of the studies ranged from 4 to 16 weeks. There were six studies mentioning data of VAS for pain comparing the use of *Curcuma longa* vs. placebo-controlled group. The remaining four studies provided the data of WOMAC total score (with each two studies comparing the use of *Curcuma longa* vs. placebo-controlled group and *Curcuma longa* vs. NSAIDs). Characteristics of the included study are shown in more detail in Table 1.

Overall, the quality of 10 RCTs was methodologically acceptable, with the majority evaluated as low risk. Eight studies mentioned using the random allocation method, while two RCTs [17-19] did not describe the method. Two RCTs were not mentioned in carrying out allocation concealment [5,21]. One study did not implement blinding in outcome measurement [24]. The evaluation results of the literature quality from the 10 RCTs included are shown in Figure 2.

Primary outcomes

1) Visual Analog Scale for pain

VAS is a validated quantitative tool used in assessing pain intensity of acute and chronic pain. This tool is presented as a

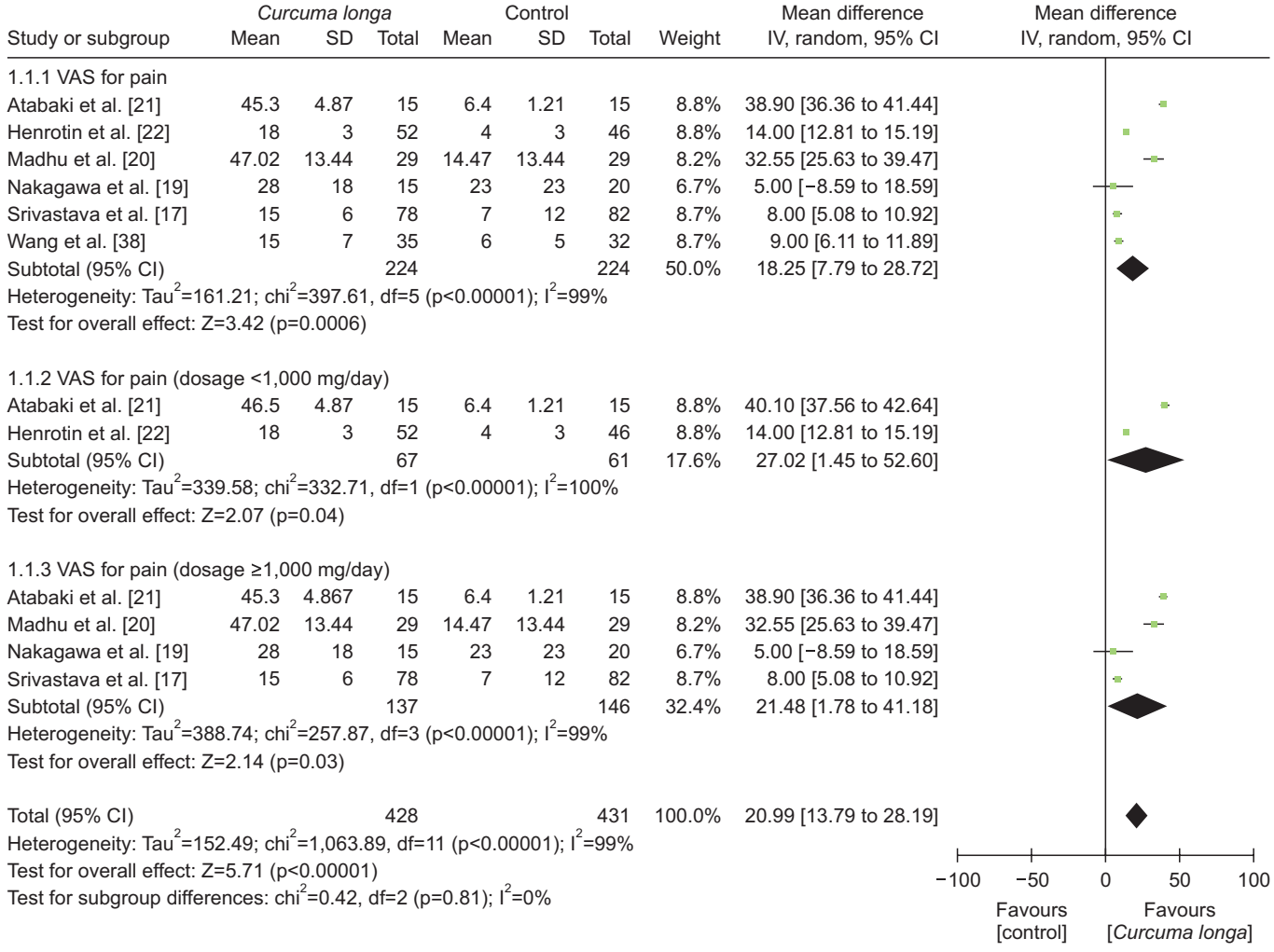

Figure 3. Forest plot portraying VAS for pain. SD: standard deviation, IV: interval variable, CI: confidence interval, VAS: Visual Analog Scale.

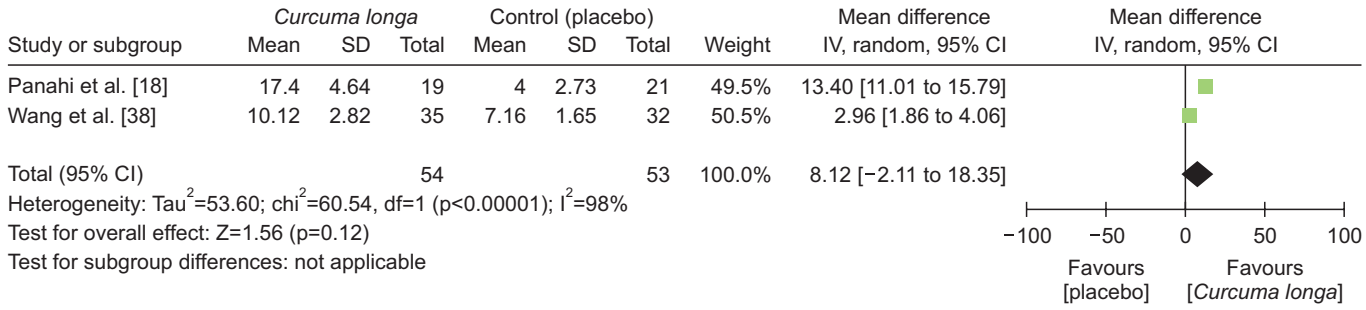

Figure 4. Forest plot portraying WOMAC total score of *Curcuma longa* vs. placebo-controlled group. SD: standard deviation, IV: interval variable, CI: confidence interval, WOMAC: Western Ontario and McMaster Universities Arthritis Index.

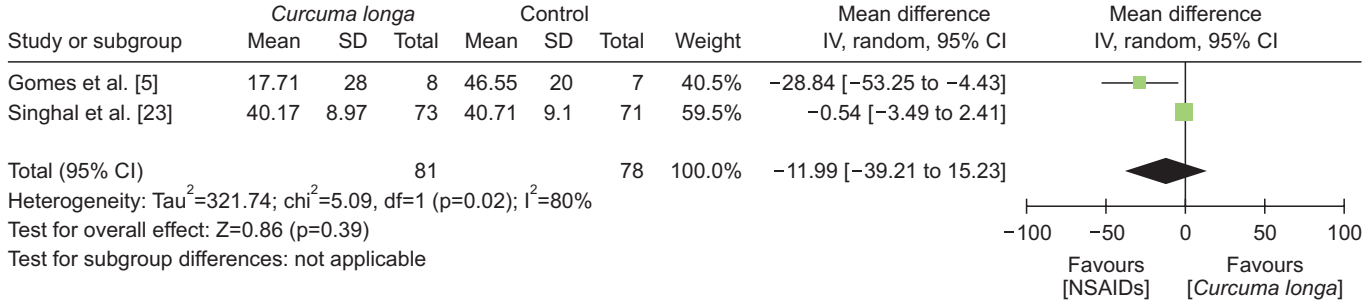

Figure 5. Forest plot portraying WOMAC total score of *Curcuma longa* vs. NSAIDs-controlled group. SD: standard deviation, IV: interval variable, CI: confidence interval, NSAIDs: nonsteroidal anti-inflammatory drugs, WOMAC: Western Ontario and McMaster Universities Arthritis Index.

Table 2. Summary evidence of adverse events

Study	Type of adverse event
Atabaki et al. [21]	No adverse events
Gomes et al. [5]	No adverse events
Henrotin et al. [22]	Abdominal discomforts, diarrhea
Madhu et al. [20]	Dyspepsia
Nakagawa et al. [19]	No serious adverse events
Panahi et al. [18]	Mild gastrointestinal symptoms
Shep et al. [24]	Nausea, diarrhea
Singhal et al. [23]	Restlessness, tingling sensation
Srivastava et al. [17]	Dyspepsia, nausea
Wang et al. [38]	One patient reported allergy but there were no severe adverse events

straight 100-mm line that has the words of "no pain" and "worst pain" from left to right-most end [25]. A total of six studies provided data relevant to VAS for pain of *Curcuma longa* extract vs. placebo. *Curcuma longa* extract was significantly more effective in the improvement of VAS for pain compared with placebo based on pooled analysis (MD: 18.25, 95% CI: 7.79 to 28.72, p=0.0006), with (I^2=99%) showing a significant heterogeneity. Whereas, subgroup analysis of different dosage of *Curcuma longa* (dose <1,000 and ≥1,000 mg/day) were both showing significant effect in the improvement of VAS for pain compared with placebo (MD: 27.02, 95% CI: 1.45 to 52.60, p=0.04), with significant heterogeneity (I^2=100%) for dose <1,000 mg/day, and (MD: 21.48, 95% CI: 1.78 to 41.18, p=0.03), with significant heterogeneity (I^2=99%) for dose <1,000 mg/day, respectively. The forest plot portraying a weighted MD with a 95% CI of VAS for pain is shown in Figure 3.

2) Western Ontario and McMaster Universities Arthritis Index total score

WOMAC is a 24-item, self-report questionnaire instrument to assess pain, physical functional disability, and joint stiffness of OA patients. Four studies provided data relevance to WOMAC total score [26,27]. *Curcuma longa* extract was more effective in improving joint function compared with placebo but was not inferior to NSAIDs based on pooled analysis performed (MD: 8.12, 95% CI: −2.11 to 18.35, p=0.12), with significant heterogeneity (I^2=98%) for placebo-controlled group and (MD: −11.99, 95% CI: −39.21 to 15.23, p=0.39), with significant heterogeneity (I^2=80%) for NSAIDs-controlled group, respectively. The forest

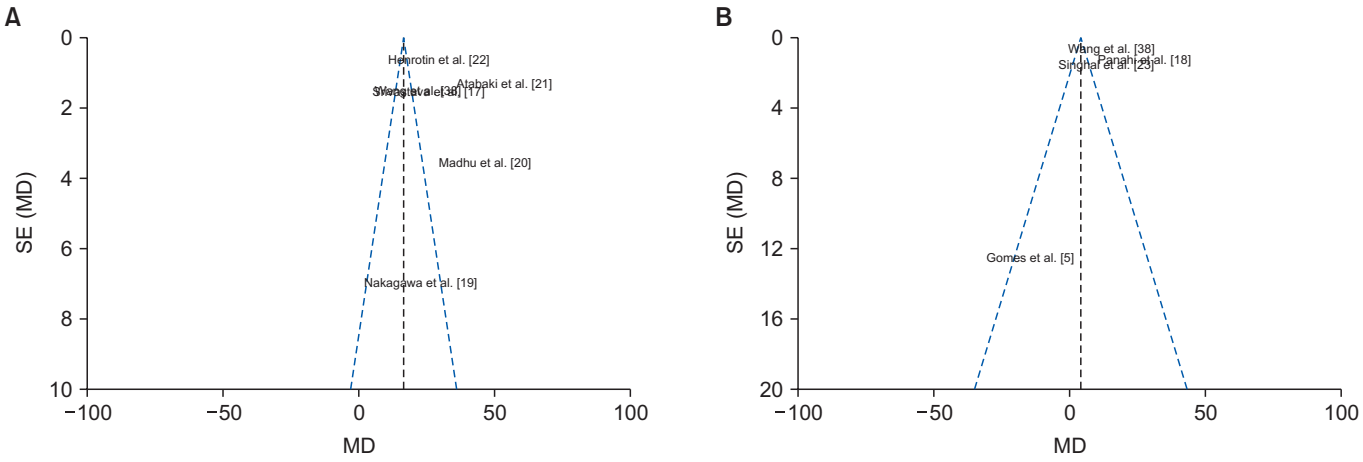

Figure 6. Funnel plot, left to right of (A) VAS for pain score, (B) WOMAC total score. VAS: Visual Analog Scale, WOMAC: Western Ontario and McMaster Universities Arthritis Index, SE: standard error, MD: mean differences.

plot portraying a weighted MD with a 95% CI of WOMAC total score for both control groups is shown in Figures 4 and 5.

Adverse events

No serious adverse events from *Curcuma longa* extract were reported in all studies. One study reported allergy to *Curcuma longa* extract that led to discontinuation of treatment. There were some mild adverse events that were found in some studies as shown in Table 2, but only few subjects across all studies experienced the minor adverse events.

Publication bias

We generated funnel plots for VAS pain score and WOMAC total score. The results of the funnel plot symmetry for both outcomes were poor, indicating a small sample effect possible or publication bias in these two indicators (Figure 6).

DISCUSSION

This metaanalysis showed the significant association of *Curcuma longa* extract to pain relief and functional improvement of knee OA when compared with placebo. The *Curcuma longa* extract is non-inferior to NSAIDs in functional improvement in WOMAC total score of knee OA patients based on our finding.

Curcuma longa is an active compound produced from *Curcuma longa's* stems. It contains yellow substances beneficial as food colouring or cooking ingredients. Recent studies have mentioned that *Curcuma longa* extract has protective effects for OA. The extract of *Curcuma longa* alleviates inflammation and decreases the oxidative stress biomarkers in knee OA [28]. It also decreases bone degradation, inhibits pit formation, and protects chondrocytes [29]. A study found that Curcumin significantly reduces the anti-inflammatory markers IL-1β, interleukin 6, and TNF-α in joint chondrocytes of human, stimulating the benefit of anti-inflammation [30]. An experimental study using a mouse model of post-traumatic OA has found that Curcumin slows the development of OA and relieves symptoms by reducing the level of matrix metalloproteinase (MMP-1, MMP-3, MMP-13), a disintegrin and metalloproteinase with thrombospondin motifs, IL-1β, and TNF-α [31]. A study has also demonstrated that Curcumin acts on key proteins in glycine, serine, and threonine metabolism, inhibiting pyruvate formation, and regulating glycolysis [30]. Curcumin was chosen because it can provide anti-inflammatory effects by suppressing the effects of $CD4^+$ cells, $CD8^+$ cells, and Th17 cells, reducing the frequency of B cells, and increasing the number of Treg cells in inflammatory areas. The Curcumin group show the TNF-α baseline decrease was statistically more significant than in the paracetamol group [23]. Curcumin also modulates Nuclear factor kappa B (NF-κβ), which inhibits cartilage degradation [32].

OA development and progression processes are affected by inflammation and oxidative stress. Impaired chondrocytes release free radicals that can destroy the segments between and components of joints (nucleic acids, protein, lipids) [33]. Curcumin are potent antioxidants in account of phenolic hydroxyl groups. Phenolic hydroxyl groups reduce lipid peroxidation and attenuate DNA and protein oxidative damage. Curcumin reduce the free radicals formation through enzyme blocking on COX-

2, 5-lipoxygenase and inducible NOS, while enhancing intracellular antioxidant defence through stimulations of nuclear factor-erythroid-2-related factor 2 [18].

The pooled analysis of our study showed significantly better pain relief for knee OA with the use of *Curcuma longa* extract. Our findings are typical to previous systematic reviews and meta-analysis by Onakpoya et al. [34] and Chen et al. [35], that found significant decrease in VAS scores in patients who received Curcumin intervention. A randomized, double-blind, placebo-controlled prospective by Nakagawa et al. [19], with 50 knee OA patients in grade II-III also showed that Curcumin group significantly improved VAS score at 8 weeks [19]. Besides the anti-inflammatory effects, Curcumin is also an antagonist nociceptin receptor, downregulating receptors of opioid-related nociceptin receptor gene 1 by 5.9-fold, which possesses a pain-relieving effect [36].

The results of our study also showed that *Curcuma longa* was more effective than placebo in functional improvement of WOMAC total score. This result was in line with a previous meta-analysis done by Dai et al. [37], which showed the efficacy of *Curcuma longa* extracts for improving joint function of knee OA patients. Moreover, a randomized, double-blind, placebo-controlled trial comprising 70 subjects of knee OA and USG-defined effusion synovitis showed that *Curcuma longa* extracts improved VAS knee pain and WOMAC pain and function over 12 weeks compared with placebo [38]. Another randomized, double-blind, placebo-controlled parallel-group trial which compared pre- vs. post-trial WOMAC scores showed a significant reduction in the WOMAC component of global ($p<0.001$) and also subscales for pain ($p<0.001$), physical function ($p<0.001$), and stiffness ($p=0.043$) scores at the end of the study in the Curcumin group. The placebo group showed no significant decrease of global and WOMAC subscales, eventhough there was a prominent decrease in the WOMAC stiffness score ($p=0.009$) [17]. Curcumin inhibits NF-κB and blocks the MMP enzymes. It prevents cartilage degradation and promotes extracellular matrix accumulation. Thus, Curcumin intensify chondrocyte existence through down-regulating the inflammation-induced apoptosis by inhibiting MMPs [18].

The results of our review when *Curcuma longa* extract was compared with NSAID directly were non-inferior in the functional improvement of OA knee patients. Similar findings were also mentioned that Curcumin was not inferior to NSAIDs in pain reduction and functional advancement for knee OA [36]. One of the basic concepts in determining the drug we choose is understanding the expected duration for the desired effect [39]. Products containing Curcuma were found to be similar in effects compared with NSAIDs and potentially to glucosamine [20,40-43]. A 4-week, multicentre study comprising 367 knee OA patients shows that *Curcuma domestica* extract was non-inferior to those receiving ibuprofen groups, with ibuprofen showing significantly higher gastrointestinal adverse events of abdominal pain/discomfort [38]. A 6-week, randomized trial of Curcuma extract, participated by 193 knee OA patients, which used paracetamol as a controlled group, showed a similar reduction ≥20% in WOMAC pain score and function/stiffness score (80% vs. 77% and 61% vs. 58%, respectively) [23]. A recent meta-analysis has verified that Curcumin/turmeric extract had treatment efficacy similar to NSAIDs based on findings from 16 RCTs and 1,810 adults [42]. Moreover, 18% of knee OA patients receiving turmeric got ≥50%, and 3% had ≥70% improvement in WOMAC pain and function/stiffness score. Compared with patients receiving paracetamol, it showed ≥50% improvement (18% vs. 0%, $p=0.0002$). Bioavailable turmeric extract improves physical joint functions and alleviates stiffness and pain as effectively as paracetamol in knee OA patients [21].

The relevant dosage of *Curcuma longa* for knee OA treatment remains uncertain. Our study establishes typical improvement in VAS for pain of the *Curcuma longa* extract treatment in different dosages of *Curcuma longa* extract: <1,000 and ≥1,000 mg/day. Similar findings were mentioned in a meta-analysis by Feng et al. [1], showing no statistically significant difference in the primary outcomes between *Curcuma longa* and placebo in all different daily doses subgroups comprising < or ≥1,000 mg/day and total doses of < or ≥50 g [1]. The plateau Curcumin levels were also equivalent in both the low and high doses of the Bio-optimized *Curcuma longa* group, which was desirable as the reason behind pain similarities from using both doses [22].

The result of our systematic review showed no serious adverse events of *Curcuma longa* extract across all studies. Safety of *Curcuma longa* has been evaluated by numerous studies with overall usage of *Curcuma longa* reported no serious adverse events when administered to OA knee patients [5,18,21,23,24]. A randomized open-label parallel-arm study with 500 mg Curcumin three times a day and 50 mg Natrium diclofenac two times a day assigned to 139 knee OA patients showed significantly less adverse effects in the Curcumin group compared to diclofenac group (13% vs. 38%, $p<0.01$). The incidence of nausea, diarrhea,

abdominal pain, and flatulence in the Curcumin group was reduced to less than 10%. Safety profile of Curcumin resulted from its gastro-protective and anti-ulcer effect [24]. NSAIDs mechanism resulted from the COX enzymes inhibition of COX-1 and COX-2, with COX-1 only inhibition resulting in adverse events. Meanwhile, Curcumin was found to inhibit the NF-κβ pathway and further decrease the formulation of COX-2. This could be the reason for fewer adverse events seen in Curcumin than in non-selective NSAIDs [34]. Although Curcumin does not cause adverse effects like NSAIDs, high doses of Curcumin can cause diarrhoea due to the cholecystokinetic effect of its ferulic and hydrofluoric acid content. Low and high doses of curcumin will reach different plateau points but provide the same clinical benefits within one month [36].

Curcumin is as effective in inflammation-related symptom improvement; it showed no significant difference between low doses (daily dose ≤1,000 mg/day or total dose ≤42 gr) and high doses (daily dose ≥1,000 mg/day or total dose ≥42 gr) in VAS pain reduction [43]. Curcumin was found to be stable once entering the bloodstream. Because of the increase pharmacokinetics and hepatoprotective activities in Curcumin use, the lower doses of these complexes might be as effective as higher doses [44,45]. The trial study of a prospective, randomized, 3-month, double-blind, placebo-controlled by Henrotin et al. [22], assessing 150 patients with knee OA showed that Curcumin level raised rapidly in treated patients and the molecule stayed at a constant level after 1 month. Moreover, *Curcuma longa* has disadvantages in poor absorption and metabolism. Therefore, some researchers work around this by combining it with piperine. Using piperine can increase Curcumin concentration in the blood, increase growth elimination time, and reduce clearance time [46].

Strengths and limitations

We included the latest ten clinical trials for this study. However, our study had several limitations. First, the studies included in this meta-analysis were heterogeneous, with the source of heterogeneity coming from multiple variations in dosages, regions, and baseline values of VAS or WOMAC of the subjects. Secondly, apparent heterogeneity was still ineradicable even after performing subgroup analyses, indicating substantial heterogeneity was not completely caused by subgrouping. Thirdly, the duration of follow-ups was only limited to 4 to 6 weeks, leaving the clinical effectiveness of *Curcuma longa* extract in long-term use unclear. According to the reasons above, more studies are needed in the future to perform comprehensive analyses better.

CONCLUSION

This study revealed that *Curcuma longa* extract has clinical application value in improving knee OA patients' pain and function and can potentially be a therapeutic option. Further rigorous studies are needed to explore optimal dosages and administration methods of *Curcuma longa* as an alternative therapy for knee OA in long term use.

SUPPLEMENTARY DATA

Supplementary data can be found with this article online at https://doi.org/10.4078/jrd.2024.0062

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CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTIONS

R.H.: conceptualization, methodology, validation, formal analysis, writing (original draft preparation), writing (review & editing), supervision and project administration. F.P.: conceptualization, methodology, validation, formal analysis, data curation, writing (original draft preparation), writing (review & editing), visualization, supervision and project administration. J.I.N.: conceptualization, methodology, formal analysis, resources, data curation, writing (original draft preparation), writing (review & editing) and visualization. A.I.M.: conceptualization, methodology, resources, data curation, writing (original draft preparation), writing (review & editing) and visualization. M.I.I.: conceptualization, methodology, resources, data curation,

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