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Clinical Significance of Curcuminoids Alone in Alleviating Pain and Dysfunction for Knee Osteoarthritis: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Abstract

Background: Curcuminoids (CURs) are the principal ingredients of *Curcuma longa L. [Zingiberaceae]* (CL)—an herbal plant used in east Asia to alleviate pain and inflammation. Thus far, the therapeutic effects of CURs for knee osteoarthritis (OA) uncovered by multiple reviews remained uncertain due to broadly involving trials with different agents-combined or CURs-free interventions. Therefore, we formed stringent selection criteria and assessment methods to summarize current evidence on the effectiveness of CURs alone in the treatment of knee OA.

Methods: A series of databases were searched for randomized controlled trials (RCTs) evaluating the efficacy of CURs for knee OA. Clinical outcomes were evaluated using meta-analysis and the minimum clinically important difference (MCID) for both statistical and clinical significance.

Results: Fourteen studies with 1633 patients were included. Overall, CURs were significantly more effective than controls in the improvements of VAS for pain (WMD: −1.46, 95% CI: −2.13 to −0.8), WOMAC total score (WMD: −7.06, 95% CI: −12.27 to −1.84), WOMAC pain score (WMD: −1.42, 95% CI: −2.41 to −0.43), WOMAC function score (WMD: −5.04, 95% CI: −7.65 to −2.43), but not in WOMAC stiffness score (WMD: −0.34, 95% CI: −0.79 to 0.1). Moreover, the effect sizes of VAS for pain and WOMAC total score exceeded their MCID, while WOMAC subscale scores did not. Additionally, CURs did not significantly increase the incidence of adverse events (AEs) compared with placebo (RR: 1.22, 95% CI: 0.89 to 1.67), and significantly lowered the incidence of AEs when compared with NSAIDs (RR: 0.71, 95% CI: 0.59 to 0.9).

Conclusions: CURs alone can be expected to achieve considerable analgesic and functional promotion effects for patients with symptomatic knee OA in short term, without inducing an increase of adverse events. However, considering the low quality and substantial heterogeneity of present studies, a cautious and conservative recommendation for broader clinical use of CURs should still be made. Further high-quality studies are necessary to investigate the impact of different dosages, optimization techniques and administration approaches on long-term safety and efficacy of CURs, so as to strengthen clinical decision making for patients with symptomatic knee OA.

Introduction

Knee osteoarthritis (OA) is one of the most general irreversible articulus diseases globally, and presents with features of incremental cartilage defect and articular space narrowing. Approximately 11.8–12.7% of the global population are affected by knee OA, according to World Health Organization [1]. The condition is similar in China, where the number of OA patients nearly increased 2.35-fold over the past three decades, and approximately 61.2 million individuals suffered from symptomatic OA in 2017, with a percentage of mild, moderate, and severe OA of 47%, 35.9%, and 17.1% respectively [2]. Despite the high prevalence of knee OA, effective and permanent interventions to halt or reverse the degenerative progression have not yet been developed [3]. Intra-articular chronic inflammation accompanied with joint pain and dysfunction is the main pathological features of knee OA, which necessitate long-term management. Widely applied pharmacotherapies aimed at anti-inflammation and pain reduction are limited to acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs) [4]. While conventional medications have only a marginal effect on pain, with no significant impact on joint function. Adverse events (AEs) that may occur in digestive and cardiovascular systems also restrict the feasibility of long-term administration of NSAIDS [5–7]. Hence, the exploration of alternative options with good safety and efficacy profiles for knee OA has been delved into traditional herbal medicine [8–10]. Notably, curcumin, extracted from the rhizome of *Curcuma longa L. [Zingiberaceae]* (CL), is a botanical extract with promising clinical values [11].

Analogues comprising curcumin, bisdemethoxycurcumin, demethoxycurcumin and cyclocurcumin are collectively referred to as curcuminoids (CURs) [12], which constitute the principal ingredients of CL—an herbal plant used in east Asia to alleviate pain and inflammation. CURs are natural polyphenols which have been shown to exert anti-inflammatory and anti-oxidant effects in vivo and vitro studies by downregulating inflammation-related nuclear factor kappa-B (NF-κB) signaling pathway, scavenging free radicals, and inhibiting the activity of enzymes, such as cyclooxygenase-2 (COX-2), 5-lipoxygenase (5-LOX), and nitric oxide synthase (NOS), which exacerbate the oxidative stress in OA condition [13–15]. Normal NSAIDS are of critical safety concerns due to simultaneously inhibition of COX-1 and COX-2 enzymes in arthritis, while CURs can reduce the synthesis of COX-2 tendentiously [16], which may result in better safety profiles. Furthermore, CURs exhibit chondroprotective properties by stimulating extracellular matrix synthesis, down-regulating the synthesis of matrix metalloproteinases (MMPs) [17]. And CURs were shown to postpone joint contracture progress via inhibiting the proliferation of myofibroblasts from the joint capsule [18]. Considering that the pathophysiology of knee OA is characterized by inflammation and degeneration with prominent symptoms of pain and dysfunction, alleviating local inflammation and oxidative stress, stimulating cartilage regeneration and delaying joint contracture may be conducive to the condition, and CURs have emerged as an attractive treatment option for knee OA.

Several animal studies have assessed the efficacy of CURs administered via nano-scale drug carriers for knee OA, demonstrating that CURs have potent anti-inflammatory and anti-arthritic activity, both with and without biological materials [19–23]. Although pre-clinical studies have revealed promising results, the clinical efficacy, safety, dosage, and treatment duration of CURs for knee OA remain equivocal. Thus far, the therapeutic effects of CURs for knee osteoarthritis (OA) uncovered by multiple reviews remained uncertain due to broadly involving trials with different agents-combined or CURs-free interventions [8, 24–26], and evidence to reveal the clinical significance of CURs alone for knee OA is insufficient. Consequently, we aimed to summarize the evidence to date on the clinical effectiveness of CURs alone in alleviating pain and dysfunction for knee OA by a systematic review and meta-analysis. We postulated that CURs have superior efficacy in pain relief and functional promotion compared to control measures.

Methods

The research was performed according to our pre-registered protocol (CRD42021266888, PROSPERO), and we adopted the concept of the minimum clinically important difference (MCID) [27] to assess the clinical significance of CURs for treating knee OA. Specific implementation process was followed the guidance of the Cochran Handbook for Systematic Review of Interventions [28] and the Preferred Reporting Items for Systematic Review and Meta-Analysis checking list (Supplementary Table 1) [29].

Literature Search

A comprehensive electronic literature retrieval was conducted by P.Y.M. and L.L.T. independently on September 2021. The Cochrane Library, Medline via PubMed, Web of Science, Embase, CNKI (China National Knowledge Infrastructure), SinoMed (Chinese BioMedical Literature Service System), Wanfang and VIP databases, and ClinicalTrials.gov (http://ClinicalTrials.gov) were searched for all published articles without time or language restriction. The search terms were as follows: (MeSH terms 'Curcumin', 'Curcuma' and related variants 'curcuminoids', 'demethoxycurcumin', 'bisdemethoxycurcumin', 'tumeric', and 'diferuloylmethane') and (MeSH terms 'osteoarthritis, knee', 'Osteoarthritis' and related variants 'knee osteoarthritis', 'KOA', 'OA') and (MeSH terms 'Randomized Controlled Trial' and related variants 'controlled clinical trial', and 'randomized') (Supplementary Table 2).

Selection Criteria

Two independent reviewers (F.X. and X.M.) fulfilled the selection process based on the following criteria: (1) participants: patients diagnosed with knee OA according to the criteria proposed by the American College of Rheumatology (ACR) [30]; (2) intervention: oral CURs; (3) control: oral conventional agents or placebo; (4) primary outcomes: visual analog scale (VAS) for pain, Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) total score, WOMAC pain score and WOMAC function score; (5) secondary outcomes: WOMAC stiffness score, withdraw rate, concomitant rescue medications, OA biomarkers and adverse events (AEs); and (6) study design: randomized controlled trials (RCTs). Studies were excluded if they met any of the following criteria: (1) duplicate publications; (2) studies with inappropriate interventions or control arms; (3) studies lacking essential data; (4) studies in which full-texts were unavailable.

Data Extraction and Quality Assessment

Literature was screened by two reviewers (L.L.T. and Z.L.) independently, and all extracted documents were recorded in Excel spreadsheets prepared in advance. Firstly, after removing duplicates using Endnote X9, the titles and abstracts of all citations were consulted for eligible RCTs. The full-texts of included RCTs were read and classified according to the selection criteria, eligible studies were involved in the qualitative and quantitative synthesis. The following contents were extracted: (1) study characteristics; (2) patient demographics; and (3) outcomes: including primary and secondary outcomes. When the data of two or more studies were originated from one clinical trial, only the latest studies providing requisite outcomes were included, and they will be regarded as one study. Attempts were made to obtain missing data by contacting the corresponding author, browsing supplementary files, or consulting relevant data from previous meta-analyses. The recommended Cochran Risk of Bias Tool 1 [31] was used to assess the risk of bias of the included studies.

Statistical Analysis

All data were processed and analyzed by J.F. and Z.L. using the Stata 14 (StataCorp, College Station, Texas, USA) and RevMan 5.4 software (The Cochrane Collaboration, Copenhagen, Denmark). Outcomes represented as continuous variables were reported as the weight mean difference (WMD) with 95% confidence interval (CI), and risk ratios (RR) with 95% CI were calculated for dichotomous outcomes. The pooled effect size with a p-value < 0.05 on two-sided t-test were defined as statistically significant. The MCID was adopted as a threshold for the pooled effect size, when the improvement of patient-reported outcomes was greater or equal to the MCID, a change in patients' management should be taken into consideration, which was defined as clinically significant. The MCID threshold for the VAS and WOMAC scores was defined as a 20% fluctuation from the baseline of the included studies according to previous researches [32-35]. Inter-study heterogeneity was assessed by c^2-based Q-test and the I^2 index, and an I^2 value of 50% was defined as the demarcation of low and high heterogeneity. Fixed-effects model was applied when there was low heterogeneity (I^2 £ 50%), and random-effects model [36, 37] was used to merge the data conservatively when the heterogeneity was unacceptable (I^2 > 50%). To explore the influence of various factors on pain and function related outcomes, we carried out pre-planned subgroup analyses for the placebo-controlled group based on daily dose of CURs (dose < 1,000 mg, or dose ³ 1,000 mg), total dose of CURs (dose < 50 g, or dose ³ 50 g), follow-up duration (time < 12 weeks, or time ³ 12 weeks), type of CURs (bio-optimized or pure extracts) and regions (Asia or non-Asia). Publication bias was detected using funnel plots and Egger's test for outcomes involving five or more comparisons. The robustness of the quantitative synthesis was tested by omitting the data of each citation in sensitivity analysis. Other outcomes that cannot be merged quantitatively were summarized as narrative reviews.

Evidence Evaluation

The quality of evidence was classified using the GRADE system [38] as high, moderate, low, or very low, with descending assignment of 4, 3, 2, or 1. As the included studies were all RCTs, the level of each outcome began as high quality, but the confidence of each evidence could be decreased by considering the following domains: (1) study limitations; (2) inconsistency of results; (3) indirectness of evidence; (4) imprecision; and (5) publication bias. When evaluating the study limitations [39], the quality of evidence could be downgraded from high level according to results of literature quality assessment, for example, if a study was defined as having unclear risk of bias when it was likely to lower confidence in the estimate of effect size, and the quality of the related outcomes would be decreased by minus 1 to moderate. The I^2 index values were used to evaluate the consistency [8, 40] grading: I^2 £ 50% equalled 'not serious' quality downgrade; 50% < I^2 £ 75% equalled 'serious' quality downgrade (minus 1); I^2 > 75% equalled 'very serious' quality downgrade (minus 2). We applied the MCID in grading imprecision for VAS and WOMAC scores on the premise that the results were not statistically significant: the 95% CI of WMD encompassed the MCID equalled 'serious' quality downgrade (minus 1); the 95% CI exceeded the MCID either in the upper or lower confidence limit equalled "very serious" quality downgrade (minus 2). The assessment of imprecision [41] for RR was implemented by strictly adhering to the GRADE guidelines. As indirectness was appraised by the stringent inclusion and exclusion criteria, reassessment was not necessary. Publication bias was evaluated according to the results of funnel plots and Egger's test.

Results

Literature Search Results

The literature screening process is illustrated in Figure 1. Initial literature retrievals obtained 401 citations, 110 of which were removed for duplicate publications. After screening the titles and abstracts of the remaining 291 citations, we excluded 262 irrelevant records based on the selection criteria. Twenty-nine studies were remained for full-text assessment, eleven studies were excluded because of ineligible interventions, including the combination of glucosamine hydrochloride, chondroitin sulphate and curcumin [42], curcumagalactomannoside complex [43, 44], CURs combined with diclofenac [45, 46], herbal formulations of different extracts [47-51], and CURs-free CL extracts [52]. Furthermore, we excluded four conference abstracts [53-56] due to incomplete data. Finally, fourteen eligible studies with 1633 patients were enrolled in our analysis [57-71].

Basic Characteristics of Studies

The study characteristics are presented in Table 1. All included studies were CURs-intervened trials aimed to evaluate the clinical effectiveness of CURs, and published between 2009 and 2021. Among which, eleven studies [57-61, 63, 64, 66, 68-72] were conducted in Asian countries, while the other three studies [62, 65, 67] were from non-Asian regions. Sample sizes were ranged from 30 to 331, and the follow-up durations were limited in 6 months. Forty-three percent of included studies [59, 62-65, 67] were founded by private corporations, 14% of included studies [19, 66, 70] declared that no founding was received, and the rest [57, 58, 60, 61, 68, 69] were founded by research departments of government or university. The details of CURs preparations and administration protocols are presented in Table 2 and Table 3. Five trials [57, 58, 64, 66, 70] applied active-controlled arms (ibuprofen, diclofenac, and paracetamol), and the other nine [59-63, 65, 67-69, 71, 72] were all placebo-controlled trials.

Quality Assessment

The results of literature quality assessment based on the Cochran Risk of Bias Tool 1 are presented in Figure 2. Overall, seven studies [57, 62, 65, 67-70] were defined as having low risk of bias, and five studies [59-61, 63, 64] were judged as having moderate risk of bias for potential reporting bias [59] and attrition bias [63], and deficiencies in specific descriptions of randomization [59, 64], allocation concealment [60] or blinding methods [59, 61, 63]. Two studies [57, 66] were judged as having high risk of bias for inadequate procedures in blind methods. An appropriate description of random sequence generation was reported in ~~eight~~ twelve studies [57, 58, 60-63, 65-70], reasonable allocation concealment was performed in thirteen studies [57-59, 61-70], and double-blinded methods were specific in nine studies [58, 60, 62, 63, 65, 67-70].

MCID for Patient-Reported Outcomes

The MCID is defined as the minimal magnitude an subjective outcome must change to achieve clinical efficacy meeting the satisfaction of patients and clinicians [27]. According to the baseline of included studies, the threshold for each outcome was calculated as follows: 1.33/10 for VAS for pain, 8.97/96 for WOMAC total score, 2.12/20 for WOMAC pain score, 6.62/68 for WOMAC function score, and 0.76/8 for WOMAC stiffness score.

Primary Outcomes

VAS for Pain

Ten studies (~~497~~ 769 patients) [57, 59-61, 63-68] assessed knee pain using VAS for pain. The overall analysis revealed that CURs had better efficacy in pain reduction than control groups (WMD: −1.46, 95% CI: −2.13 to −0.8, P < 0.001, Figure 3), with high heterogeneity (I^2 = 90.6%). The relative improvement (−1.46) of VAS for pian exceeded the MCID (1.33 for VAS for pain) . When compared to placebo, CURs were found to be more efficacious on the improvement of VAS for pain (WMD: −1.94, 95% CI: −2.65 to −1.22, P < 0.001, I^2 = 86.3%). Whereas there was no significant difference detected between CURs and NSAIDs (WMD: −0.3, 95% CI: −0.63 to 0.04, P = 0.082, I^2 = 6.3%). For the comparison between CUR and NSAIDs, the therapeutic effect (−0.3) was smaller than the MCID. However, the therapeutic effect (−1.94) of CURs in placebo-controlled group exceeded the MCID with both statistical and clinical significance.

An obvious decrease from 86.3% to 36.3% in heterogeneity for placebo-controlled group was observed after removing the study of Atabaki et al. [68], with the intervention of CURs loaded nano-micelles, the pooled result (WMD: −1.50, 95% CI: −1.85 to −1.15, P < 0.001) was similar with the original analysis. Sensitivity analysis did not ferret out one individual study that would affect the statistical robustness of the overall results.

WOMAC Total Score

Seven study (795 patients) [58, 60, 62-64, 69, 70] reported the data of WOMAC total score. The overall analysis found that CURs were more efficacious than control groups on functional promotion (WMD: −7.06, 95% CI: −12.27 to −1.84, P < 0.001, Figure 4), with high heterogeneity (I^2 = 87.9%). The relative improvement (−7.06) of WOMAC total score did not exceed the MCID (8.97 for WOMAC total score). When compared to placebo, CURs were found to be more efficacious on the improvement of WOMAC total score (WMD: −10.47, 95% CI: −15.65 to −5.3, P < 0.001, I^2 = 0.0%). Whereas there was no significant difference found between CURs and NSAIDs (WMD: −0.68, 95% CI: −3.88 to 2.52, P = 0.676, I^2 = 80.6%). For the comparison between CURs and NSAIDs, the therapeutic effect (−0.68) did not exceed the MCID, while the effect size (−10.47) of CURs in placebo-controlled group was larger than the MCID with both statistical and clinical significance.

When the data of Haroyan et al. [62] was omitted, a significant reduction in heterogeneity from 80.6% to 0.0% in placebo-controlled group was observed, but the pooled result (WMD = −12.88, 95% CI: −14.79 to −10.98, P < 0.001) of remained studies was similar with the original analysis. Sensitivity analysis did not ferret out one individual study that would affect the statistical robustness of the overall results.

WOMAC Pain Score

Eight studies (956 patients) [58, 60-63, 67, 69, 70] reported the data of WOMAC pain score. The overall analysis indicated that CURs were significantly better than control groups in terms of pain relief (WMD: −1.42, 95% CI: −2.41 to −0.43, P = 0.005, Figure 5), with high heterogeneity (I^2 = 85.6%). The relative improvement (−1.42) of WOMAC pain score did not exceed the MCID (2.12 for WOMAC pain score). When compared to placebo, CURs were found to be significantly more efficacious on the improvement of WOMAC pain score (WMD: −1.94, 95% CI: −2.91 to −0.97, P < 0.001, I^2 = 79.2%, Figure 4). There is no significant difference detected between CURs and NSAIDs (WMD: 0.24, 95% CI: −0.47 to 0.96, P = 0.505, I^2 = 0.0%, Figure 4). For the comparison between CURs and NSAIDs, the therapeutic effect (0.24) did not exceed the MCID. Similarly, the effect size (−1.94) of CURs in placebo-controlled group was smaller than the MCID with only statistical significance.

The study of Srivastava et al. [61] was considered to be the potential source of heterogeneity given that the I^2 values in placebo-controlled group decreased from 79.2% to 51.8% after omitting their data, and the pooled result (WMD: −2.28, 95% CI: −3.05 to −1.52, P < 0.001) reached up to the magnitude exceeding the threshold (2.12) for clinical significance. Sensitivity analysis did not ferret out one individual study that would affect the statistical robustness of the overall results.

WOMAC Function Score

Eight studies (~~481~~ 956 patients) [58, 60-63, 67, 69, 70] assessed joint function using the WOMAC function score. The overall analysis displayed a significantly better efficacy of functional promotion in CURs groups (WMD: −5.04, 95% CI: −7.65 to −2.43, P < 0.001, Figure 6), with high heterogeneity (I^2 = 83.6%). The relative improvement (−5.04) of WOMAC function score did not exceed the MCID (6.62 for WOMAC function score). When comparing to placebo, CURs were found to be significantly more efficacious on the improvement of WOMAC function score (WMD: −6.36, 95% CI: −8.94 to −3.78, P < 0.001, Figure 5). However, there is no significant difference found between CURs and NSAIDs (WMD: −0.57, 95% CI: −3.07 to 1.94, P = 0.657, I^2 = 0.0%, Figure 4). For the comparison between CURs and NSAIDs, the therapeutic effect (−0.57) did not exceed the MCID. Similarly, the effect size (−6.36) of CURs in placebo-controlled group was smaller than the MCID with only statistical significance.

After excluding the study of Haroyan et al. [62], the inter-study heterogeneity in placebo-controlled group slightly decreased from 79.2% to 70.7%, but the pooled result (WMD: −7.21, 95% CI: −9.71 to −4.72, P < 0.001) reached up to the magnitude exceeding the threshold (6.62) for clinical significance. Sensitivity analysis did not ferret out one individual study that would affect the statistical robustness of the overall results.

WOMAC Stiffness Score

Eight studies (956 patients) [58, 60-63, 67, 69, 70] evaluated joint stiffness status using the WOMAC stiffness score. The pooled analysis found no significant difference between CURs and control groups in relieving joint stiffness (WMD: −0.34, 95% CI: −0.79 to 0.1, P = 0.131, Figure 7), with high heterogeneity (I^2 = 80.7%). The effect size (−0.34) of WOMAC stiffness score did not achieve statistical significance in overall analysis, and the 95% CI encompassed the MCID (0.76/8 for WOMAC stiffness score). However, when compared with placebo, CURs were found to be significantly more efficacious on the improvement of WOMAC stiffness score (WMD: −0.54, 95% CI: −1.03 to −0.05, P = 0.031, I^2 = 77.6%, Figure 6). There is no significant difference found between CURs and NSAIDs (WMD: 0.19, 95% CI: −0.17 to 0.56, P = 0.298, I^2 = 0.0%, Figure 4). For the comparison between CURs and NSAIDs, the therapeutic effect (0.19) did not exceed the MCID. Similarly, the effect size (−0.54) of CURs in placebo-controlled group was smaller than the MCID with only statistical significance.

By excluding the study of Panda et al. [63], a decrease in heterogeneity from 77.6% to 0.0% in placebo-controlled group was observed, but the pooled result (WMD: −0.31, 95% CI: −0.56 to −0.05, P = 0.018) was similar with the original analysis. Sensitivity analysis did not ferret out one individual study that would affect the statistical robustness of the overall results.

Secondary Outcomes

OA biomarkers

Two studies [60, 61] assessed the antioxidation of CURs through detecting the serum level of reactive oxygen species (ROS), superoxide dismutase (SOD), glutathione (GSH) and malondialdehyde (MDA), and found that changes in these biomarkers may contribute to the therapeutic effects of CURs in alleviating OA symptoms. Three studies [61, 64, 72] reported the serum level of inflammatory mediators, such as interleukin-1β (IL-1β), IL-4, IL-6, tumor necrosis factor-α (TNF-α), leukotriene B4 (LTB4) and prostaglandin E2 (PGE2), and proved that the systemic anti-inflammatory effects of CURs may have no correlation with its therapeutic effects in knee OA. Besides, six studies [62-64, 66, 68, 72] measured the C-reactive protein (CRP) serum concentration and erythrocyte sedimentation rate (ESR), two sensitive biomarkers for systemic inflammation. Two studies [64, 65] evaluated the status of cartilage degeneration via serum level of C-terminal telopeptides of type II Collagen (U-CTX-II) and ColI2-1. Similarly, there was no significant difference found between groups for aforementioned biomarkers.

Withdraw Rate and Rescue Medications

All included studies reported the withdraw rate of follow-up cohort, there was no lost case reported in the treatment and control group of the study of Atabaki et al. [68], thus their data cannot be merged in meta-analysis. The pooled analysis showed no significant difference in withdraw rate between CURs and placebo group (RR: 1.12, 95% CI: 0.76 to 1.64, P = 0.57, I^2 = 0.0%) or NSAIDs group (RR: 0.87, 95% CI: 0.63 to 1.21, P = 0.4, I^2 = 14.2%, Supplementary Figure 1). Eight studies [58-60, 63, 65-67, 69] reported the administration of concomitant rescue medications for ethical concerns. Among which, five studies [58, 63-66] reported the number of patients using rescue medications, the pooled analysis found no significant difference in the usage of rescue medications between CURs and placebo group (RR: 0.93, 95% CI: 0.6 to 1.43, P = 0.742, I^2 = 55.4%) or NSAIDs group (RR: 0.99, 95% CI: 0.53 to 1.83, P = 0.963, I^2 = 38.8%,

Supplementary Figure 2). Four studies [59, 60, 67, 69] recorded the discontinuation of rescue medications, the pooled results showed that the cessation rate of rescue medications in CURs group was significantly higher than placebo group (RR: 4.04, 95% CI: 2.43 to 6.71, P < 0.001, I^2 = 11.7%, Supplementary Figure 2).

Adverse Events

Among the included fourteen studies, two [68, 69] reported no AEs at the end of the trials. According to the data of the remaining twelve studies (1515 patients), AEs were mainly concentrated in gastrointestinal symptoms including meteorism, gastro-oesophageal reflux, dyspepsia, nausea, and stomach pain as shown in Table 4. The pooled analysis revealed no significant difference between CURs and control groups (RR: 0.86, 95% CI: 0.72 to 1.04, P = 0.122, Figure 8), with low heterogeneity (I^2 = 49.2%). There was no significant difference found in the incidence of AEs between CURs and placebo group (RR: 1.22, 95% CI: 0.89 to 1.67, P = 0.227, I^2 = 34.7%), while a significant lower incidence of AEs was observed in CURs group when compared with NSAIDs group (RR: 0.71, 95% CI: 0.57 to 0.90, P = 0.004, I^2 = 55.8%).

Subgroup analysis

Subgroup analyses were only performed in the placebo-controlled group due to limited number of original studies, and to avoid the interference of different controls to the results. The results of subgroup analyses are arranged in Table 5. We found no significant difference in the subgroup results of VAS for pain, WOMAC pain score and WOMAC function score compared to the overall analyses, except for the pure extracts subgroup; the result of the subgroup showed no significant difference between CURs and placebo on the improvement of WOMAC pain score. As for clinical significance, the effect size of the pure extracts and non-Asia subgroups decreased to be lower than the MCID for VAS for pain. Conversely, in the time < 12 weeks, daily dose < 1,000 mg, total dose < 50 g, bio-optimized extracts, and Asia subgroups, we found that the effect sizes increased to exceed the MCID for WOMAC pain score and WOMAC function score.

Publication bias

The Egger's linear regression test for VAS for pain, WOMAC total score, WOMAC pain score, WOMAC function score and WOMAC stiffness score did not detect significant publication bias (P = 0.296, 0.96, 0.78, 0.515, and 0.63 respectively), however, asymmetry of funnel plots was observed by visual inspection, which indicating the existence of potential publication bias (Supplementary Figure 3).

Discussion

Knee OA is a whole joint disease arising from active dynamic changes in the balance between regeneration and destruction of articular tissues, not just a simple passive process getting worse with age [73]. The progression of knee OA is accompanied by complex pathological changes, like arthritis, synovitis, abnormal cartilage/bone metabolism, angiogenesis and neurogenesis in subchondral bone, which eventually lead to destruction of joint structure and cause various symptoms related to joint disorders [74]. According to data of a global burden of disease (GBD) study [75] in 2015, knee OA accounted approximately 85% of the GBD of OA. Pain and dysfunction were the leading causes for medical care use and clinical decision making. Novel disease-modifying treatments targeting the pathological process of OA are in development to solve the treatment dilemma of symptom-relieving drugs (pain-killers or NSAIDs) [76]. Among which, natural plant drugs and their extracts with multi-target effects have attracted much attention of medical researchers and clinicians [8-10].

CURs, a group of natural polyphenols extracted from the rhizome of CL, have been shown to possess therapeutic effects on knee OA as a result of their anti-inflammatory and anti-oxidant properties [15]. Previous studies have demonstrated that the regulation of inflammation- and catabolism-related pathways via the inhibition of pro-inflammatory cytokines, enzymes, and transcription factors is the main mechanism underlying the anti-inflammatory and chondroprotective properties of CURs [77]. Indeed, multiple studies [78-80] have shown that CURs can attenuate the secretion of pro-inflammatory cytokines, such as IL-1β, IL-6, TNF-α, and PGE2, in chondrocytes, which may result in pain reduction. Meanwhile, it has been indicated that CURs can alleviate the chronic inflammatory conditions of knee OA by inhibiting the activation of transcription factor NF-κB and the synthesis of NF-κB-modulated MMP and COX-2 [81]. Moreover, CURs possess anti-oxidant properties to redress oxidant stress status by blocking enzymes related to the formation of free radicals and strengthening the intra-articular defense response for oxidant stress [13].

Recently, it has been indicated that the progression of joint contracture can be retarded by CURs through inhibiting the myofibroblast proliferation-related PI3K/Akt/mTOR signaling pathway [18]. Meanwhile, CURs were also found to perform chondroprotective effects via PI3K/Akt/mTOR pathway by alleviating TNF-α induced inflammation, enhancing autophagy and decreasing apoptosis [82]. Consequently, CURs can promote the function of knee OA through chondroprotective effects by accumulating extracellular matrix and preventing cartilage damage, and delaying joint contracture. Thus far, many pre-clinical and clinical studies [83] have identified CURs as being effective for treating knee OA.

Discussion of main results

The principal finding of our study was that CURs were associated with better effectiveness than placebo and not inferior to NSAIDs in terms of pain reduction and functional promotion for knee OA. The pooled analyses found that CURs were more effective than placebo in the improvement of VAS for pain, WOMAC total score, WOMAC pain score, WOMAC function score and WOMAC stiffness score, while there was no significant difference found between CURs and NSAIDs. Moreover, we used the MCID as a threshold to assess the clinical significance of the difference between CURs and the control groups. The minimal clinical benefits that can be perceived by patients and practitioners are defined as the MCID, which can be calculated by anchor-based and distribution-based methods. We applied the anchor-based method to set the threshold at 20% based on previous research [27, 32-35]. As a result, we found that only VAS for pain and WOMAC total score achieved clinical significance by exceeding their MCID, while WOMAC pain score, WOMAC function score and WOMAC stiffness score did not. We also found that CURs did not induce an increase of AEs compared with placebo, and CURs were associated with

significant lower incidence of AEs when compared with NSAIDs. The total incidences of AEs in CURs and control groups were 26.09% and 36.67%. Diarrhea and/or constipation (5.8% versus 8.46%) were the most frequent mild AEs in CURs and control groups (Table 4).

Despite the highly pleiotropy in knee OA, the application of CURs is controversial due to poor oral bioavailability. Numerous studies have focused on methods to optimize the pharmacokinetics of CURs [84]. Among the included studies, ten used bioavailable CURs, the preparation techniques can be roughly summarized into four categories: (1) modulating metabolism via adjuvants (piperine or turmeric oils) [60, 62, 66, 70]; (2) phospholipid or liposome complexes [63, 64]; (3) nanoparticles or nano-capsules [59, 68, 69]; and (4) emulsifying agents [65], while the other four used pure extracts from CL. Theoretically, bio-optimized CURs should be superior to pure extracts given their higher absorptivity and lower metabolism [84]. According to our study, we found that the result of the bio-optimized extracts subgroup increased to exceed the MCID of WOMAC pain score, but the result of the pure extracts subgroup was neither statistically nor clinically significant. Besides, the effect sizes of both VAS for pain and WOMAC function score in the bio-optimized extracts subgroup exceeded their MCID, while those in the pure extracts group did not. These findings indicated that bio-optimized CURs may have better clinical applicability for knee OA than pure CURs. However, a recent meta-analysis of Wang et al. [24] found no significant difference between the enhanced and normal CL extracts in pain and physical function related outcomes. Two trials [45, 66] applying normal CURs as adjuvants to NSAIDs were included in their placebo-controlled group for quantitative synthesis, which may cause the divergence in the priority of the enhanced CURs given that the added effects of NSAIDS were neglected. Each study in our meta-analysis applied different metrics and tactics to remodel the bioavailability, more direct comparisons between various CURs products with different bio-optimization techniques are essential to verify our results and seek a cost-effective agent. Predictably, bio-optimization techniques with more than one approach to conquer the hindrances (e. g., poor water solubility, rapid metabolism, and instability) to oral bioavailability would achieve significant improvement in the effectiveness of CURs. What's more, the possibility of local administration like intra-articular injection of CURs should be taken into consideration for OA condition is mainly characterized by intra-articular inflammation rather than systemic inflammation.

The appropriate dosage of CURs for treating knee OA remains uncertain. Previous meta-analyses by Daily et al. [10] and Onakpoya et al. [9] demonstrated the typical dose of 1,000 mg/day as effective in the improvement of inflammation-related symptoms. According to our study, there was no statistically significant difference in the main outcomes between CURs and placebo in all subgroups of different doses (daily dose < or ³ 1,000 mg and total dose < or ³ 50 g). Theoretically, the optimal dose of a drug is closely associated with its safety and bioavailability. Various studies focused on diverse diseases have proved that CURs are effective without major safety concerns even at high doses such as 6 g/day [85], which indicated that the main limitation of optimal dosage is the bioavailability of CURs. Thus theoretically, the requirement for CURs of lower dosage and better compliance without affecting curative effects for knee OA may be met by the optimization of bioavailability. Actually, we found that the effect sizes of VAS for pain, WOMAC pain score and WOMAC function score in low-dose (daily dose < 1,000 mg and total dose < 50 g) subgroup exceeded their MCID, while those in high-dose (daily dose ³ 1,000 mg and total dose ³ 50 g) subgroup did not achieve clinical significance. The observed difference in clinical values between low- and high-dose subgroup may be caused by the limited number of studies in each subgroup or the administration of bio-optimized CURs for all studies in low-dose group.

A recently published review by Zeng et al. [26] suggested that CURs could not exhibit significant therapeutic effects until the duration of administration lasted for more than 12 weeks. Given the simultaneous inclusion of active-controlled [45, 57, 58, 66, 86] and placebo-controlled trials in their subgroup analyses, the effect sizes at different time points may be weakened by effects of NSAIDs-controlled arms. Thus, we removed the data of active-controlled trials in subgroup analyses, and found that CURs showed favorable improvement in VAS for pain, WOMAC pain score, and WOMAC function score compared to placebo at each time points (follow-up duration < or ³ 12 weeks). Besides, the MCID was exceeded by the effect sizes of all main outcomes in the time < 12 weeks subgroup, but the effect sizes of the WOMAC pain score and WOMAC function score in the time ³ 12 weeks subgroup did not achieve clinical significance. The reason for the difference in clinical values between short- and long-term subgroup may be that all three studies [60, 63, 69] in the short-term subgroup applied bio-optimized CURs, and two [61, 67] of the three [61, 62, 67] studies in long-term subgroup used normal CURs. Overall, in terms of alleviating pain and other symptoms, bio-optimized CURs may be sufficiently potent to lower dosage and shorten medication cycle. Besides, larger effect sizes with clinical significance of both pain reduction and functional promotion were observed in trials performed in Asia compared with those in other countries, which was in accordance with the result of a recently published review by Wang et al. [24].

The quality of our findings was evaluated using the GRADE system [38]. All pain and function related outcomes were downgraded to have a low quality of evidence duo to inconsistency caused by the substantial heterogeneity among studies, while AEs were defined as high-quality evidence (Supplementary Table 3). The US Food and Drug Administration (FDA) defined CURs as nutraceuticals under "Generally Recognized as Safe" (GRAS) [87], and good safety and tolerability properties have been revealed by multitudinous studies at cellular level, in animals and even in human subjects [85], but it is still worth noting that nutraceuticals like CURs generally lack a systemic safety assessment before being used for medicinal purposes [88], and the blood level of CURs is easy to be increased to exceed the safe effective concentration with the rapid upgrades on extraction and biological optimization methods, therefore the potential dose- and time-dependent side effects of CURs on human body should be weighted carefully when facing the current benefits and potential values for broader clinical use of CURs.

Strengths and limitations

In this study, we included the latest fourteen clinical trials focused on this topic. Meanwhile, trials with ineligible interventions (CURs-free extracts, complexes, or adjuvants to active treatments) were excluded to realize a more objective display of the therapeutic effect of CURs for knee OA. Besides, the clinical significance of CURs in alleviating pain and dysfunction for knee OA was also evaluated by the MCID of patient-reported outcomes. However, the limitations of our study should be considered when interpreting our findings. Firstly, the quality of the original studies was low, and substantial heterogeneity was detected among the included studies, and the exact sources of heterogeneity were hard to be found for which may stem from the multitudinous variations in dosages, follow-up durations, regions, preparation schemes of CURs, and baseline values. Secondly, obvious heterogeneity was still present after subgroup analyses, the insufficient number of studies in each subgroup weakened the confidence level of our results, and prevented us from conducting a dose-response analysis.

Thirdly, despite the promising chondroprotective effects of CURs, only one study [67] assessed the cartilage compositional change by MRI T2 relaxation time and found no significant positive effect. Fourthly, the durations of follow-ups in main outcomes were limited to within 6 months, as a result, the long-term clinical effectiveness of CURs remains equivocal. Although Egger's test did not indicate significant publication bias, the limited data volume of included studies made the linearity assessment quite uncertain and at risk of being overly influenced by single studies, and the asymmetry of funnel plots observed by visual inspection also indicated the existence of potential publication bias. Because the symmetry of funnel plots could be influence by various factors, such as publication bias, and/or small-study effects, it was difficult to figure out the cause of asymmetry, especially when the sample size of each comparison was less than ten [89]. For the reasons above, further studies are needed to warrant our findings and perform more comprehensive analyses.

Conclusion

CURs alone can be expected to achieve considerable analgesic and functional promotion effects for patients with symptomatic knee OA in short-term, without inducing an increase of adverse events. However, considering the low quality and substantial heterogeneity of present studies, a cautious and conservative recommendation for broader clinical use of CURs should still be made. Further high-quality studies are necessary to investigate the impact of different dosages, optimization techniques and administration approaches on long-term safety and efficacy of CURs, so as to strengthen clinical decision making for patients with symptomatic knee OA.

Declarations

Ethics Approval and Consent to Participate

Not applicable.

Consent for Publication

Not applicable.

Availability of data and materials

All data generated or analyzed during this study are included in this article [and its supplementary information files].

Competing interests

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Author Contributions

Jie Feng, Panyun Mu and Yimei Hu participated in the conceptualization of the study and drafted the protocol. Panyun Mu and Linling Tian carried out the literature search. Study selection was done by Feng Xiong and Xu Ma. Data Extraction and quality assessment were finished by Linling Tian and Zhao Li. Statistical analysis and evidence evaluation were conducted by Jie Feng and Zhao Li. The manuscript was drafted by Jie Feng and modified by Yimei Hu. All authors read and approved the final version of this paper.

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Tables

Table 1 The basic characteristic of included studies

Study	Region	Outcomes	Treatment		Sample size (female/male)		Age (years)		K–L grade	Follo up dura
			Intervention	Control	Intervention	Control	Intervention	Control		
Kuptniratsaikul V 2009	Thailand	VAS, AEs	CLextract	Ibuprofen	52 (41/11)	55 (45/10)	61.4 ± 8.7	60.0 ± 8.4	-	6 we
Kuptniratsaikul V 2014	Thailand	WOMAC, AEs	CL extract	Ibuprofen	171 (157/14)	160 (139/21)	60.30 ± 6.8	60.9 ± 6.9	1-4	4 we
Nakagawa Y 2014	Japan	VAS, AEs,Inflammatory Biomarkers	Nano-curcumin (Theracurmin®)	Placebo	18 (14/4)	23 (18/5)	66.10 ± 7.2	71.9 ± 5.3	2-3	8 we
Panahi Y 2014 Panahi Y 2015 Rahimnia AR 2015	Iran	VAS, WOMAC, AEs, Inflammatory Biomarkers	Curcuminoids (C3 complex®)	Placebo	19 (14/5)	21 (17/4)	57.32 ± 8.78	57.57 ± 9.05	-	6 we
Srivastava S 2016	India	VAS, WOMAC, AEs, Inflammatory Biomarkers	CL extract (Haridra®)	Placebo	78 (53/25)	82 (50/32)	50.23 ± 8.08	50.27 ± 8.63	1-4	4 mon
Haroyan A 2018	Armenia	WOAMC, AEs, laboratory indicators	Curcuminoids (CuraMed®)	Placebo	66 (60/6)	68 (65/3)	54.65 ± 8.84	56.04 ± 8.55	1-3	12 week
Panda SK 2018	India	VAS, WOMAC, AEs, Inflammatory Biomarkers	Curcuminoids (Curene®)	Placebo	25	25	55.2 ± 8.58	53.12 ± 8.25	2-3	2 mon
Gupte PA 2019	India	VAS, AEs, Inflammatory Biomarkers	Curcumin (Longvida®)	Ibuprofen	17 (11/6)	25 (23/2)	57 ± 7.5	54.0 ± 8.0	1-4	3 mon
Herotin Y 2019	Belgium	VAS, AEs, Inflammatory Biomarkers	Curcumin (FLEXOFYTOL®)	Placebo	47 (40/7) 49 (39/15)	45 (34/11)	61.4 ± 7.49 60.9 ± 9.78	63.3 ± 7.69	2-4	6 mon
Shep D 2019	India	VAS, AEs, Inflammatory Biomarkers	Curcuminoids (BCM-95®)	Diclofenac	70 (25/45)	69 (21/48)	53.09 ± 4.17	52.14 ± 3.76	-	4 we
Wang Z 2020	Australia	VAS, WOMAC, AEs, MRI	CL extract (Turmacin Plus)	Placebo	36 (18/18)	34 (21/13)	61.3 ± 8.5	62.4 ± 8.8	-	12 week
Atabaki M 2020	Iran	VAS, AEs, Inflammatory Biomarkers	Nano-curcumin (SinaCurcumin®)	Placebo	15 (15/0)	15 (15/0)	49.13 ± 5.81	48.26 ± 5.11	2-3	3 mon
Hashemzadeh K 2020	Iran	WOMAC, AEs, Inflammatory Biomarkers	Nano-curcumin (SinaCurcumin®)	Placebo	36 (29/7)	35 (31/4)	54.11 ± 5.8	56.54 ± 5.77	2-3	6 we
Singhal S 2021	India	WOAMC, AEs	Curcuminoids (BCM-95®)	Paracetamol	73 (53/20)	71 (54/17)	53.1 ± 10.9	50.8 ± 9.9	2-3	6 we

CL Curcuma longa L., *VAS* visual analog scale, *WOMAC* Western Ontario and McMaster Universities osteoarthritis index, *AEs* adverse events, *MRI* magnetic resonance imaging, *K–L* Kellgren–Lawrence, *BMI* body mass index

Table 2 Characteristics of curcuminoids formulations applied in the included studies

Studies	Formulations	Source	Compounds or species, concentration	Purity or encapsulation rate (%)	Quality control reported? (Y/N)	Chemical analysis reported? (Y/N)
Kuptniratsaikul V 2009	CL extract	Thai Government Pharmaceutical Organization	Curcuminoidsextracted from the dried rhizomes ofCL, 250 mg per capsule	Not mention	Y – Prepared according to the Good Manufacturing Procedures Standard	N
Kuptniratsaikul V 2014	CL extract	Thai Government Pharmaceutical Organization	Curcuminoidsextracted from the dried rhizomes ofCL, 250 mg per capsule	75% – 85%	Y – Prepared according to the Good Manufacturing Procedures Standard	Y – HPLC
Nakagawa Y 2014	Theracurmin®	Theravalues, Tokyo, Japan	Surface-controlled water-dispersible nano-curcumin, 30 mg percapsule	Not mentioned	N	N
Panahi Y 2014 et al.	C3 complex®	Sami Labs Ltd., Bangalore, India	Curcuminoids and bioperine, 500 mgand 5mg percapsule	Not mentioned	N	N
Srivastava S 2016	Haridra®	Himalaya Drug Company Bangalore, India	Curcuminoids extracted from rhizomes of CL, 500 mg per capsule	³95%	N	Y – HPTLC
Haroyan A 2018	CuraMed®	EuroPharma, USA	Curcuminoids and volatile oil extracted from rhizomes of CL, 500mg and 49–52 mg per capsule	Not mentioned	Y – Prepared according to the Good Manufacturing Practice	N
Panda SK 2018	Curene®	Olene Life Sciences Pvt. Ltd., Chennai, India	Curcuminoids and volatile oil extracted from rhizomes of CL, 500mg per capsule	³95%	Y– Developed using proprietary technology called Aqueosome®	N
Gupte PA 2019	Longvida®	Verdure Sciences, USA	Solid lipid curcumin particles containing 400 mg patented lipophilic matrix and 80 mg curcumin percapsule	Not mentioned	Y – Made with SLCP™ Technology	N
Herotin Y 2019	FLEXOFYTOL®	Tilman SA, Baillonville, Belgium	Curcuminoids extracted from extracted from rhizomes of CL, polysorbate 80 [E433]as an emulsifier, and citric acid [E330] as an acidity regulator, 46.67 mg percapsule	Pharmaceutical-grade	N	N
Shep D 2019	BCM-95®	Arjuna Natural Ltd., Kerala, India	Curcuminoids and volatile oil extracted from rhizomes of CL, 500 mg per capsule	³95%	N	N
Wang Z 2020	Turmacin Plus	Natural Remedies Pvt., Bengaluru	Curcuminoids and turmerosaccharides extracted from rhizomes of CL, 500 mg per capsule	20%	N	N
Atabaki M 2020	SinaCurcumin®	Exir Nano Sina Company, Tehran, Iran	Nanomicelle consists of curcumin, 80 mg per capsule	»100%	N	N
Hashemzadeh K 2020	SinaCurcumin®	Exir Nano Sina Company, Tehran, Iran	Nanomicelle consists of curcumin, 80 mg per capsule	»100%	N	N
Singhal S 2021	BCM-95®	Arjuna Natural Pvt. Ltd., India	Curcuminoids and volatile oil extracted from rhizomes of CL, 500 mg per capsule	³95%	N	Y – UPLC, FT-NIR spectrometer

*CL*Curcuma longa L., *HPLC*high-performance liquid chromatography, *HPTLC* high-performance thin layer chromatography, *UPLC* ultra-performance liquid chromatography, *FT-NIR spectrometer*, Fourier transform near infrared spectrometer

Table 3 Administration protocols of curcuminoids and rescue medications for patients of included studies

Studies	Dose (mg/time)	Frequency (time/day)	Daily dose*(mg/day)	Total dose†(g)	Rescue medications
Kuptniratsaikul V 2009	500	4	2000	84	
Kuptniratsaikul V 2014	500	3	1500	42	Tramadol
Nakagawa Y 2014	90	2	180	10.08	Celecoxib
Panahi Y 2014 et al.	500	3	1500	63	Naproxen
Srivastava S 2016	500	1	500	60	Diclofenac
Haroyan A 2018	500	3	1500	126	
Gupte PA 2019	80	2	160	14.4	
Panda SK 2018	500	1	500	30	Paracetamol
Herotin Y 2019 a	93.34	2	186.68	33.6	Paracetamol / NSAIDs
Herotin Y 2019 b	140.01	2	280.02	50.4	
Shep D 2019	500	3	1500	42	Paracetamol
Wang Z 2020	500	2	1000	84	Paracetamol
Atabaki M 2020	80	1	80	7.2	Diclofenac
Hashemzadeh K 2020	40	2	80	3.36	
Singhal S 2021	500	2	1000	42	

* The daily dose of curcuminoids is equal to the product of the dose and frequency † The total dose of curcuminoids is equal to the product of the daily dose and follow-up duration

Table 4 The incidence of adverse events in curcuminoids and control groups

Groups	Curcuminoids group		Control group	
Adverse events	Total (n)	Incidence (%)	Total (n)	Incidence (%)
Dyspepsia	33	4.35	38	5.03
Nausea	24	3.16	52	6.88
Stomach pain	37	4.87	26	3.44
Diarrhea and/or constipation	44	5.80	60	7.94
Meteorism and gastro-esophageal reflux	21	2.77	31	4.10
Impairment of liver and/or kidney function	1	0.13	1	0.13
Others	38	5.01	52	6.88
Summary	198	26.09	260	34.39

Table 5 Subgroup analyses of VAS for pain, WOMAC pian score and WOMAC function score in curcuminoids versus placebo group

Outcomes	VAS for pain			WOMAC pain score			WOMAC function score		
Subgroups	Studies	WMD (95% CI)	I^2(p-value)	Studies	WMD (95% CI)	I^2(p-value)	Studies	WMD (95% CI)	I^2(p-value)
Overall analysis	7	-1.94 (-2.65,-1.22)	86.3% (p<0.001)	6	-1.94 (-2.91,-0.97)	79.2% (p<0.001)	6	-6.36 (-8.94,-3.77)	79.2% (p<0.001)
Daily dose of curcuminoids									
Dose<1,000 mg	4	-2.16 (-3.45,-0.88)	89.9% (p<0.001)	2	-2.84 (-3.46, -2.22) ‡	0.0% (p = 0.629)	2	-8.74 (-10.17,-7.31)§	86.2% (p<0.001)
Dose³1,000 mg	3	-1.57 (-2.38,-0.77)	72.6% (p = 0.026)	4	-1.25 (-2.06,-0.43)	47.2% (p = 0.128)	4	-4.47 (-6.63, -2.31)	55.3% (p = 0.135)
Total dose of curcuminoids									
Dose<50 g	4	-2.37 (-3.91,-0.83)	92.3% (p<0.001)	2	-2.84 (-3.46, -2.22) ‡	0.0% (p = 0.629)	2	-8.74 (-10.17,-7.31)§	0.0% (p = 0.667)
Dose³50 g	4	-1.51 (-2.16,-0.86)	59.2% (p = 0.061)	4	-1.25 (-2.06,-0.43)	47.2% (p = 0.128)	4	-4.47 (-6.63, -2.31)	42.7% (p = 0.155)
Follow-up duration									
Time<12 weeks	3	-1.78 (-2.49, -1.08)	61.5% (p = 0.074)	3	-2.83 (-3.43, -2.23) ‡	0.0% (p = 0.884)	3	-8.83 (-10.23,-7.24)§	0.0% (p = 0.763)
Time³12 weeks	4	-2.04 (-3.38,-0.71)	91.2% (p<0.001)	3	-1.05 (-1.83,-0.28)	44.1% (p = 0.167)	3	-4.08 (-5.51, -2.65)	0.0% (p = 0.372)
Biological optimization									
Bio-optimized extracts	5	-2.25 (-3.33,-1.17)	88.0% (p<0.001)	4	-2.38 (-3.33, -1.43) ‡	61.4% (p = 0.051)	4	-7.45 (-11.40,-3.51)§	83.1% (p = 0.001)
Pure extracts	2	-1.28 (-1.63, -0.29) †	0.0% (p = 0.345)	2	-1.09 (-2.45, 0.27)*	70.0% (p = 0.068)	2	-4.74 (-6.45, -3.04)	0.0% (p = 0.925)
Regions									
Asia	5	-2.32 (-3.29,-1.34)	91.5% (p<0.001)	4	-2.19 (-3.65, -0.74) ‡	86.5% (p<0.001)	4	-7.80 (-10.64,-4.96)§	75.1% (p = 0.007)
Non-Asia	2	-1.14 (-1.76, -0.51) †	0.0% ((p = 0.704)	2	-1.45 (-2.25,-0.65)	0.0% (p = 0.391)	2	-3.08 (-5.32,-0.85)	0.0% (p = 0.411)

WMD weighted mean difference, *CI* confidence interval

* The result of the subgroup was inconsistent with the overall analysis of WOMAC pain score for not achieving statistical significance

† The effect size of the specific subgroups decreased to be lower than the MCID (1.33) of VAS for pain

‡ The effect size of the specific subgroups increased to exceed the MCID (2.12) of WOMAC pain score

§ The effect size of the specific subgroups increased to exceed the MCID (6.62) of WOMAC function score

Figures

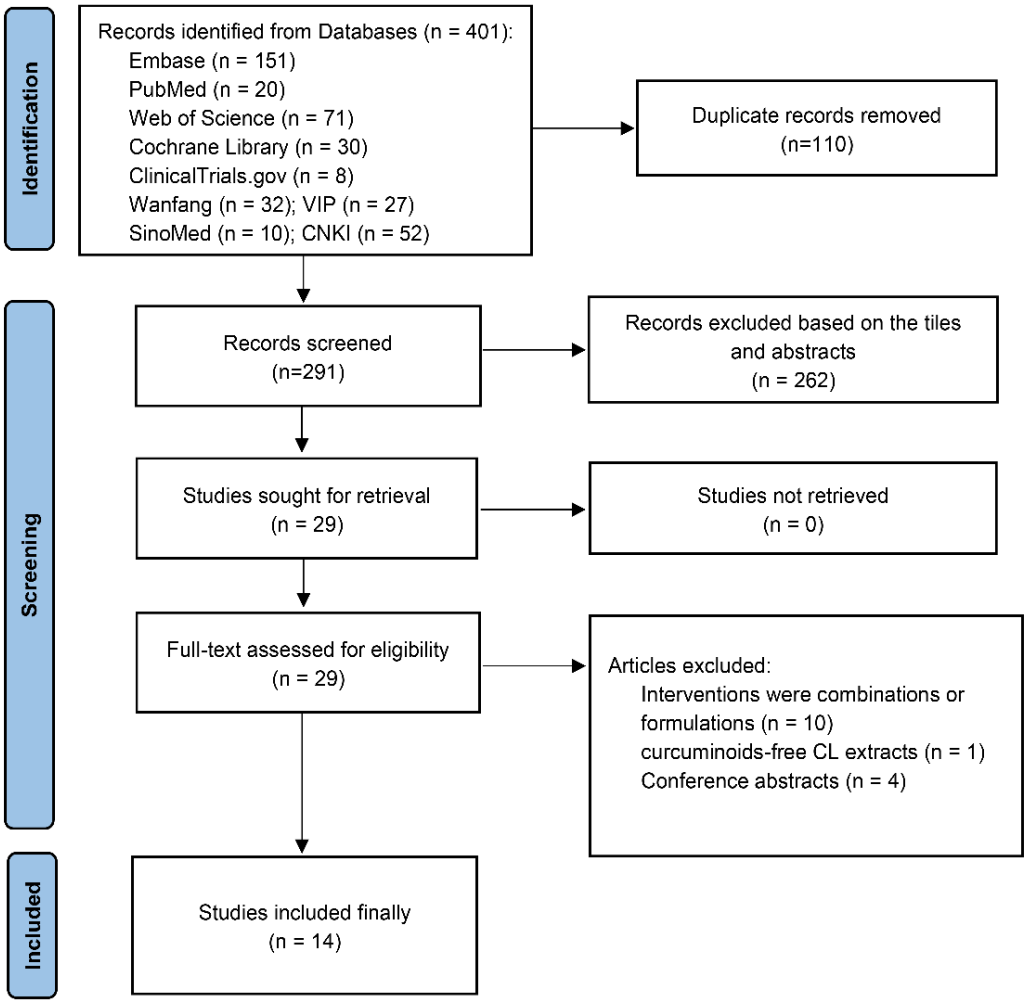


Figure 1

Flow chart of literature screening.

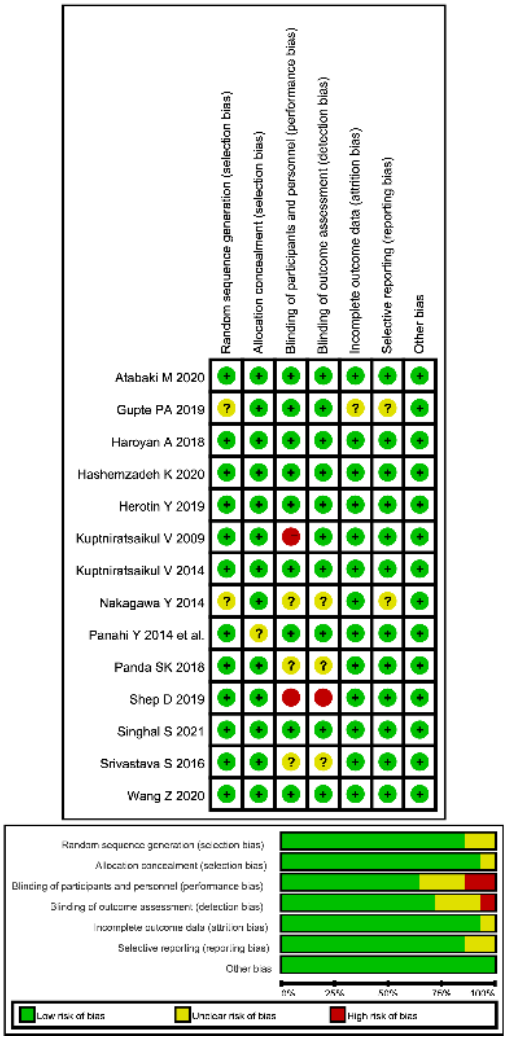


Figure 2

Risk of bias summary.

Figure 3

Forest plot portraying the weighted mean difference with 95% confidence interval of VAS for pain.

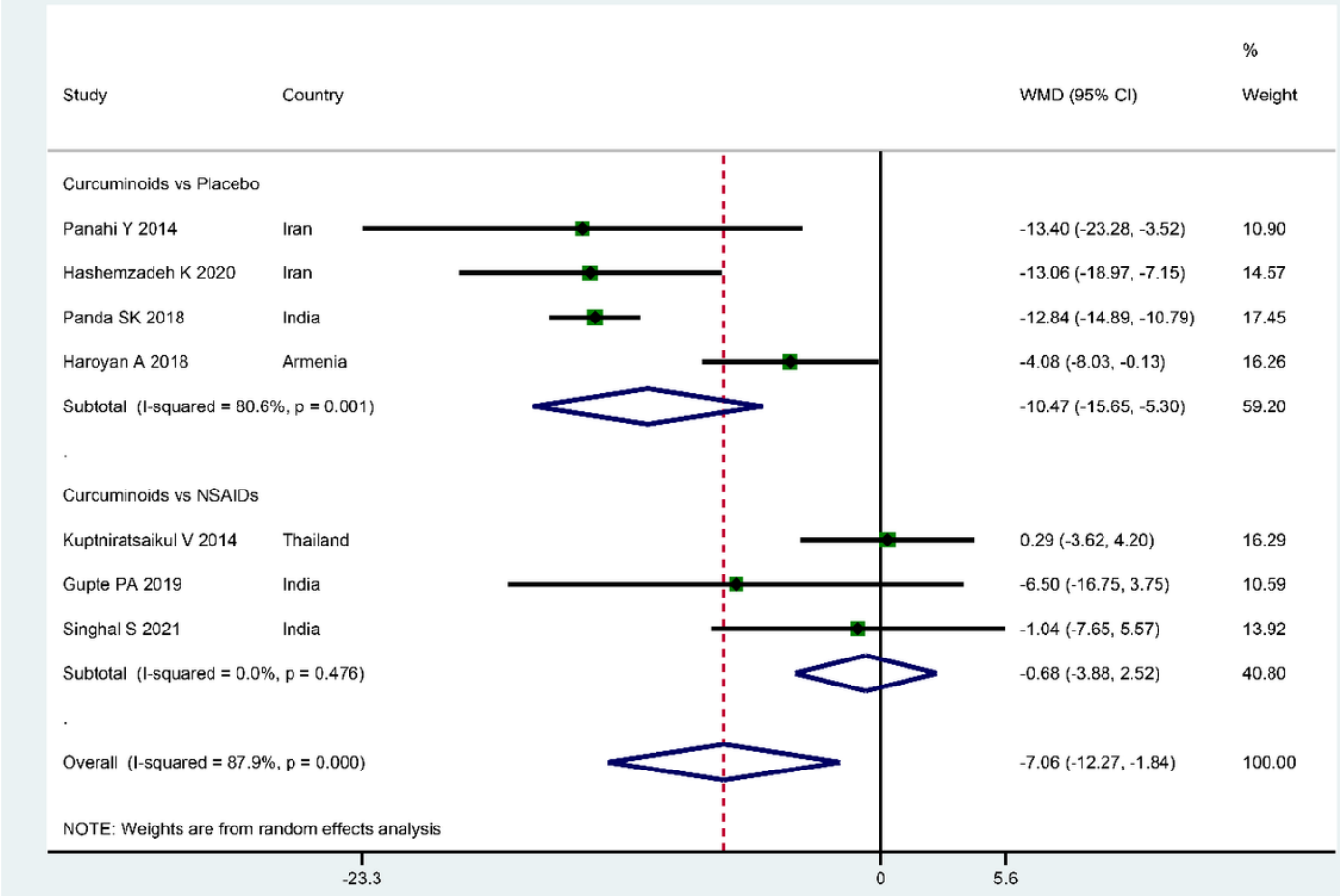


Figure 4

Forest plot portraying the weighted mean difference with 95% confidence interval of WOMAC total score.

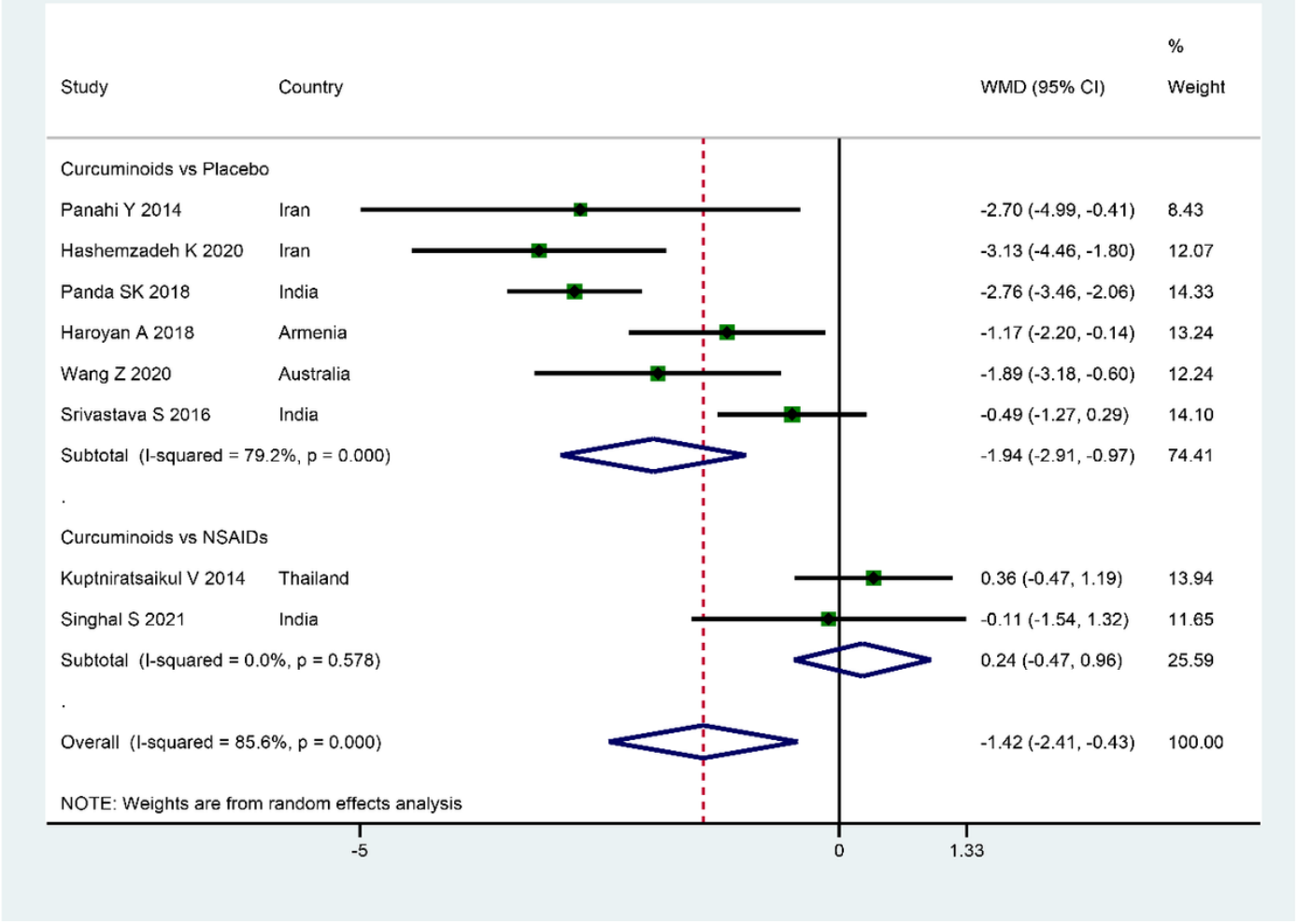


Figure 5

Forest plot portraying the weighted mean difference with 95% confidence interval of WOMAC pain score.



Figure 6

Forest plot portraying the weighted mean difference with 95% confidence interval of WOMAC function score.

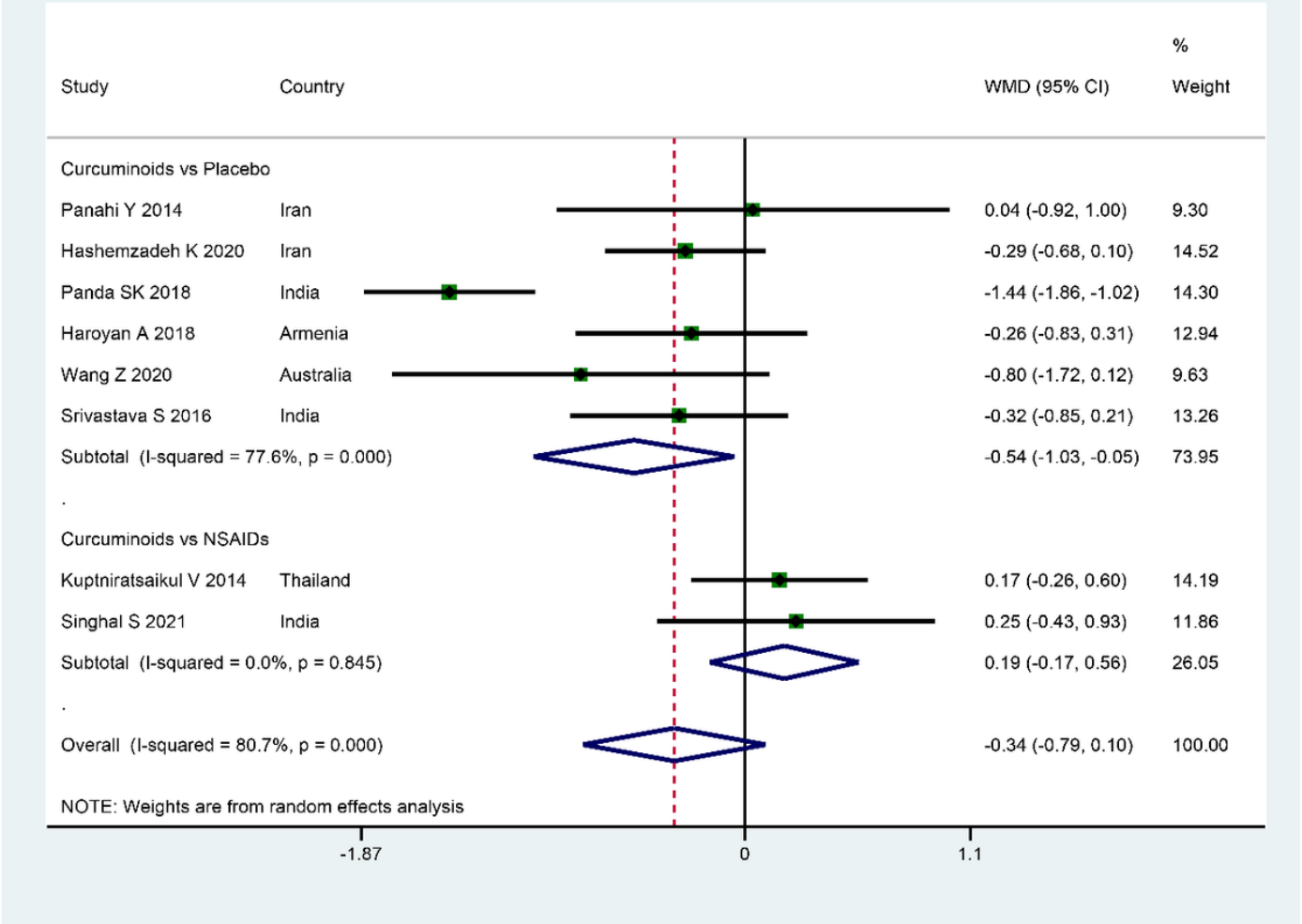


Figure 7

Forest plot portraying the weighted mean difference with 95% confidence interval of WOMAC stiffness score.

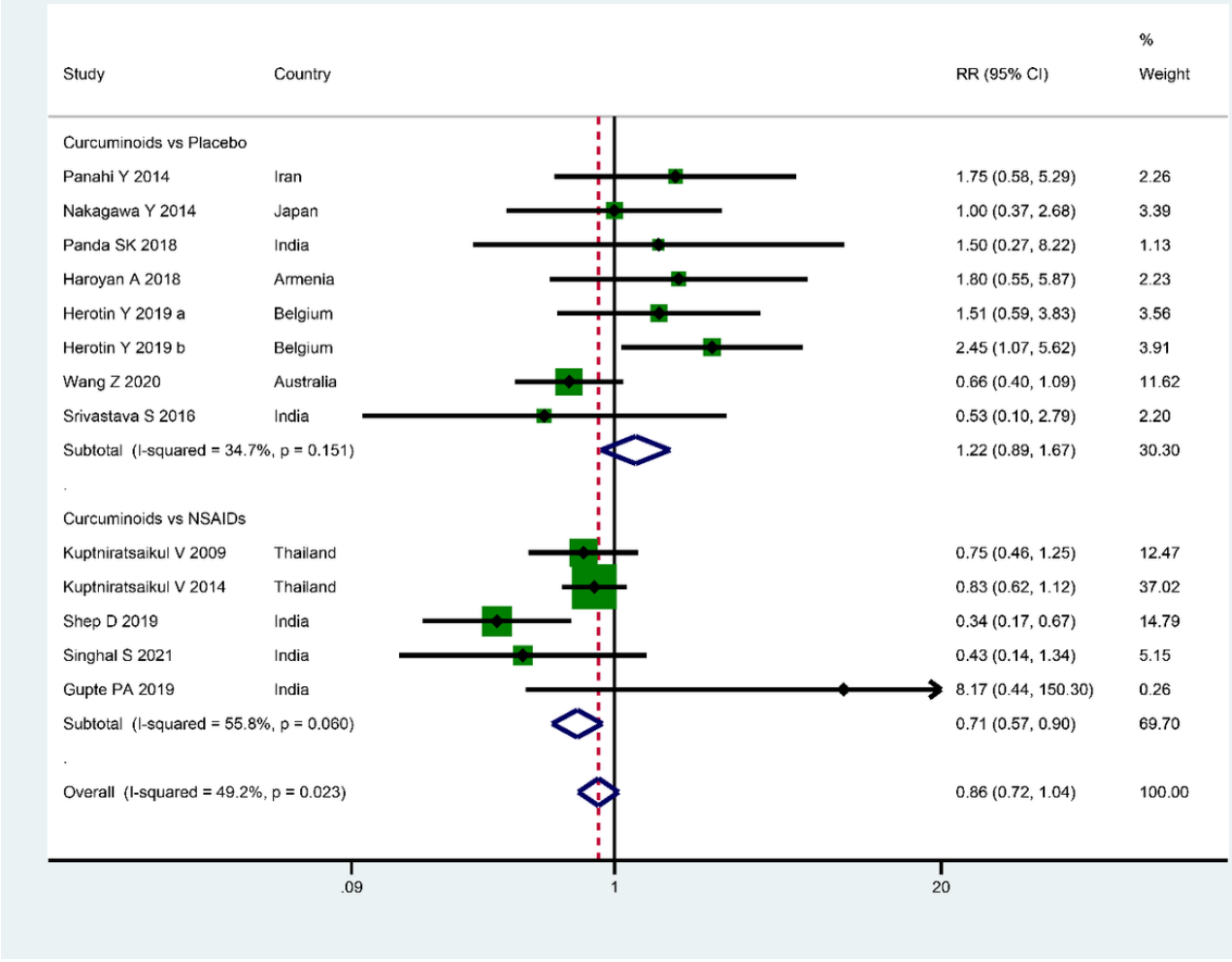


Figure 8

Forest plot portraying the risk ratio with 95% confidence interval of adverse events.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryFigures.pdf
- SupplementaryTable1PRISMA2020checklist.xlsx
- SupplementaryTable2SearchstrategysampleofPubMed.docx
- SupplementaryTable3GRADEqualityassessmentofevidence.docx