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Review Article

Analgesic Efficacy and Safety of Curcuminoids in Clinical Practice: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Abstract

Background. Curcuminoids are natural products with potent anti-inflammatory and antioxidant properties. There have been a number of reports on the analgesic effects of curcuminoids in clinical trials, yet data have not been fully conclusive.

Objectives. To provide the highest level of evidence on the efficacy of curcuminoids in patients with painful conditions through meta-analysis of data from randomized controlled trials (RCTs).

Methods. A systematic review and meta-analysis was conducted using data reported by RCTs. The primary efficacy measure was pain intensity or algofunctional status. Treatment effect was summarized with standardized mean difference (SMD) calculated from differences in means of pain measures between treatment and control groups using a random-effects model.

Results. A total of eight RCTs met our inclusion criteria that included 606 randomized patients. Curcuminoids were found to significantly reduce pain (SMD: −0.57, 95% CI: −1.11 to −0.03, $P = 0.04$). This pain-relieving effect was found to be independent of administered dose and duration of treatment with curcuminoids, and was free from publication bias. Curcuminoids were safe and well tolerated in all evaluated RCTs.

Conclusion. Curcuminoids supplements may be a safe and effective strategy to improve pain severity, by warranting further rigorously conducted studies to define the long-term efficacy and safety.

Key Words. Pain; Curcumin; Curcuminoids; Meta-Analysis; Effect Size

Key points

- This paper is the first meta-analysis on the analgesic effect of curcuminoids.
- Curcuminoids may be safe and effective to relieve pain in different disease conditions.
- This pain-relieving effect is independent of administered dose and duration of treatment and was free from publication bias.

Introduction

Curcumin (diferuloyl methane) is the principal curcuminoid of the popular Indian spice turmeric. This polyphenolic compound has been identified as the active ingredient of turmeric. It possesses various

pharmacological activities including anti-inflammatory [1,2], antioxidant [3,4], anti-proliferative [5], and anti-angiogenic properties [6]. Curcumin has a large range of molecular targets including transcription factors, growth factors and their receptors, cytokines, enzymes, and genes regulating cell proliferation and apoptosis. These mechanisms of action have been extensively described in previous systematic reviews [7,8]. Since curcumin has powerful antioxidant and anti-inflammatory effects, it can serve as a potential treatment for a variety of human diseases. In fact, the efficacy of curcumin has been shown in several clinical trials and against a diverse range of diseases including colorectal cancer [9], pancreatic cancer [10], solid tumors [11,12], inflammatory bowels disease [13], depression [14], osteoarthritis [15,16], hypertriglyceridemia [17], and cardiometabolic [18,19], respiratory [20,21], and neurodegenerative diseases [22]. However, the low bioavailability of curcumin is regarded as a major challenge for the optimal effectiveness of curcumin in clinical setting [23]. Major reasons contributing to low plasma and tissue levels of curcumin appear to be limited intestinal absorption, extensive intestinal glucoronidation, rapid metabolism, and rapid systemic elimination [24]. Orally administrated curcumin is rapidly converted to curcumin glucuronides and curcumin sulfates or reduced to hexahydrocurcumin in the intestine and the liver [25]. Metabolic derivatives of curcumin do not possess the same biological activity as the original compound [23]. Serum concentration of intact curcumin administrated orally to healthy volunteers peaks 1–2 hours after an oral dose in human subjects with peak serum concentrations of 0.5, 0.6, and 1.8 μM at massive doses of 4, 6, and 8g/day, respectively [26].

There is a need for improvement of the formulation of curcumin to enhance the systemic bioavailability of this phytochemical. To improve the bioavaibility of curcumin, numerous approaches have been undertaken. These approaches have been described by Anand et al. in a comprehensive review [23]. In summary, these approaches involve the use of 1) adjuvants like piperine that inhibit hepatic and intestinal glucuronidation [27]; 2) liposomal delivery systems, which can carry both hydrophilic and hydrophobic molecules [28]; 3) nano-sizing techniques [7]; 4) phophoslipid complexes of curcumin [29]; structural analogues of curcumin [30]; and 5) polysorbate as an emulsifier [31].

Many clinical trials have reported an analgesic effect of curcuminoids in different states including postsurgical pain [26], osteoarthritis [15,32,33], fibromyalgia [34], gout [34] and rheumatoid arthritis [35]. This analgesic effect was explained by curcumin capacity 1) to inhibit PGE2 production via the inhibition of COX-2 gene expression, 2) to stimulate cortisol production by adrenal gland by inhibiting the bTREK-1 potassium channels, and 3) to deplete nerve endings of the neurotransmitter substance *P* [36–40]. Analgesic effects of curcumin have also been shown in a number of human studies [15,32,34,35,41–44], but the results have not been fully conclusive owing to the inter-study variations in terms of design, dosage, size of studied population, and the method of pain assessment. Hence, there is a need to estimate the overall effect size of curcuminoids in relieving pain and the significance of this pooled effect. In order to clarify the debate around the efficacy of curcuminoids in pain alleviation, we undertook a meta-analysis restricted to clinical trials with the lowest risk of bias. Indeed, such a combined analysis is considered to provide the highest level of evidence available for evaluating an intervention.

Methods

Search Strategy

This study was designed according to the guidelines of the 2009 preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement [45]. SCOPUS (http://www.scopus.com) and Medline (http://www.ncbi.nlm.nih.gov/pubmed) databases were searched using the following search terms in titles and abstracts [also in combination with Medical Subject Heading (MeSH) terms]: (curcumin OR curcuminoid OR *Curcuma*) AND (pain OR painful OR painless OR VAS OR "visual analogue scale" OR nociception OR anti-nociceptive OR antinociceptive OR relaxation OR relaxant OR relaxing OR anesthetic OR anaesthetic OR anesthesia OR anaesthesia OR relief OR relieving OR discomfort OR myalgia OR hyperalgesia). The wild-card term ''*'' was used to increase the sensitivity of the search strategy. No language restriction was used in the literature search. The search was limited to studies in human. The literature was searched from inception to September 4, 2014. Selected articles were hand searched to identify further relevant studies.

Study Selection

Original studies were included if they met the following inclusion criteria: 1) be a randomized controlled trial in either parallel-group or cross-over design; 2) investigated the impact of curcuminoids or curcuminoid-containing extracts on any measure of pain; 3) applied a numerical measure of pain severity—for example, visual analog scale (VAS); and 4) presented sufficient information on pain severity at baseline and at the end of study in both curcuminoid and control groups. Exclusion criteria were 1) non-clinical studies, 2) uncontrolled trials, 3) using non-standardized extracts of turmeric or other *Curcuma* species,; 4) using essential oils or curcumin-free extracts of *Curcuma* species, 5) using topical preparations of curcuminoids, and 6) lack of sufficient information on baseline or follow-up pain severity.

Data Extraction

Eligible studies were reviewed and the following data were abstracted: 1) first author's name; 2) year of publication; 3) study location; 4) number of participants in the curcuminoid and control groups; 5) underlying

disease, 6) age, gender, and body mass index (BMI) of study participants; 7) method of pain severity assessment; 8) duration of pain; and 9) prevalence of smoking, type 2 diabetes, dyslipidemia, hypertension, and CHD.

Quality Assessment

The quality of included studies was assessed using Jadad scale [46]. This scale encompasses randomization (0–2 points), blinding (0–2 points), and dropouts and withdrawals (0–1 point). The overall score of a study according to this scale ranges between 0 and 5, with higher scores indicative of a better quality [46]. Studies with Jadad scores of <3 and ≥ 3 were considered as low and high quality, respectively. Two investigators independently assessed the quality of studies and controversies were resolved through discussion.

Quantitative Data Synthesis

Meta-analysis was conducted using Review Manager, version 5.2 (Cochrane Collaboration) and Comprehensive Meta-Analysis (CMA) V2 software (Biostat, NJ) [47]. Standard deviations (SDs) of the mean difference were calculated using the following formula: SD = square root $[(SD_{pre\text{-}treatment})^2 + (SD_{post\text{-}treatment})^2 - (2R \times SD_{pre\text{-}treatment} \times SD_{post\text{-}treatment})]$, assuming a correlation coefficient (R) = 0.5. In case of reporting SEM, SD was estimated using the following formula: SD = SEM × sqrt (*n*), where *n* is the number of subjects. In case of reporting median and range, mean and SD values were estimated using the method described by Hozo et al. [48].

Net changes in measurements (change scores) were calculated for parallel and cross-over trials, as follows: (measure at end of follow-up in the treatment group − measure at baseline in the treatment group) − (measure at end of follow-up in the control group − measure at baseline in the control group). A random-effects model and the generic inverse variance method were used to compensate for the heterogeneity of studies in terms of curcuminoids formulation used (bioavailability-improved or unformulated), dose of curcuminoids, trial design (parallel or cross-over), duration of curcuminoids supplementation, and demographic characteristics of individual trials (underlying disease, age, gender, etc). Standardized mean differences (SMDs)—expressed as Hedges' *g*—along with 95% confidence intervals (CIs) were used as summary statistics owing to the use of different indices for the evaluation of pain severity in the included studies. Effect sizes for lipid changes were expressed as weighed mean difference (WMD) and 95% confidence interval (CI). For safety analyses, risk ratios (RR) and 95% confidence intervals were calculated using the Mantel-Haenszel method [49]. In order to evaluate the influence of each study on the overall effect size, sensitivity analysis was conducted using the one-study remove (leave-one-out) approach [50,51]. The power of analysis to detect statistically significant difference between statin and control groups was computed using the PS software [52].

Publication Bias

Potential publication bias was explored using visual inspection of Begg's funnel plot asymmetry. Duval & Tweedie "trim and fill" method was used to adjust the analysis for the effects of publication bias [53].

Meta-Regression

Random-effects meta-regression was performed using mixed-effects (unrestricted maximum likelihood) method to evaluate the association between calculated SMDs and dose and duration of curcuminoid supplementation in individual studies.

Results

Flow of Included Studies

The electronic search provided 1,044 articles. Of those, 48 were scrutinized as full texts and eight articles were finally selected to be included in the analysis. The reasons for excluding the remaining 40 articles were lack of assessment of a numerical index of pain severity [n = 18], lack of standardization of extracts for curcuminoids (n = 3), not having a RCT design (n = 14), using curcumin-free extract (n = 1), not being an original research article (n = 1), and not providing sufficient data on pain severity (n = 3) (Figure 1). The final meta-analysis included a total of 606 subjects; 306 in the curcuminoid and 300 in the control group. Table 1 shows the baseline characteristics of the included studies.

Characteristics of Included Studies

Out of the eight included RCTs, three were conducted in patients with knee osteoarthritis [15,32,43], while other trials recruited patients with active rheumatoid arthritis [35], acute muscle injury [44], tropical pancreatitis [42], breast cancer receiving radiotherapy [41], and patients undergoing laparoscopic cholecystectomy [26]. The population size of trials ranged between 15 [35] and 331 [43]. Females were predominant in the included trials apart from two studies [42,44]. All trials were randomized, of which four had a double-blind [15,26,41,42] and four had a single-blind [32,35,43,44] design. In five studies, the control group received placebo [15,26,41,42,44], while three studies had an active control group receiving ibuprofen [32,43] or sodium diclofenac [35]. Duration of supplementation with curcuminoids ranged between 4 days [44] and 8 weeks [35]. Six studies used purified curcuminoids for supplementation [15,26,35,41,42,44], while two studies used *Curcuma domestica* extracts with known amounts of curcuminoids [32,43]. Overall, daily dose of purified curcuminoids in the included trials ranged between 400 [44] and 6,000 mg [41]. In order to address the low oral

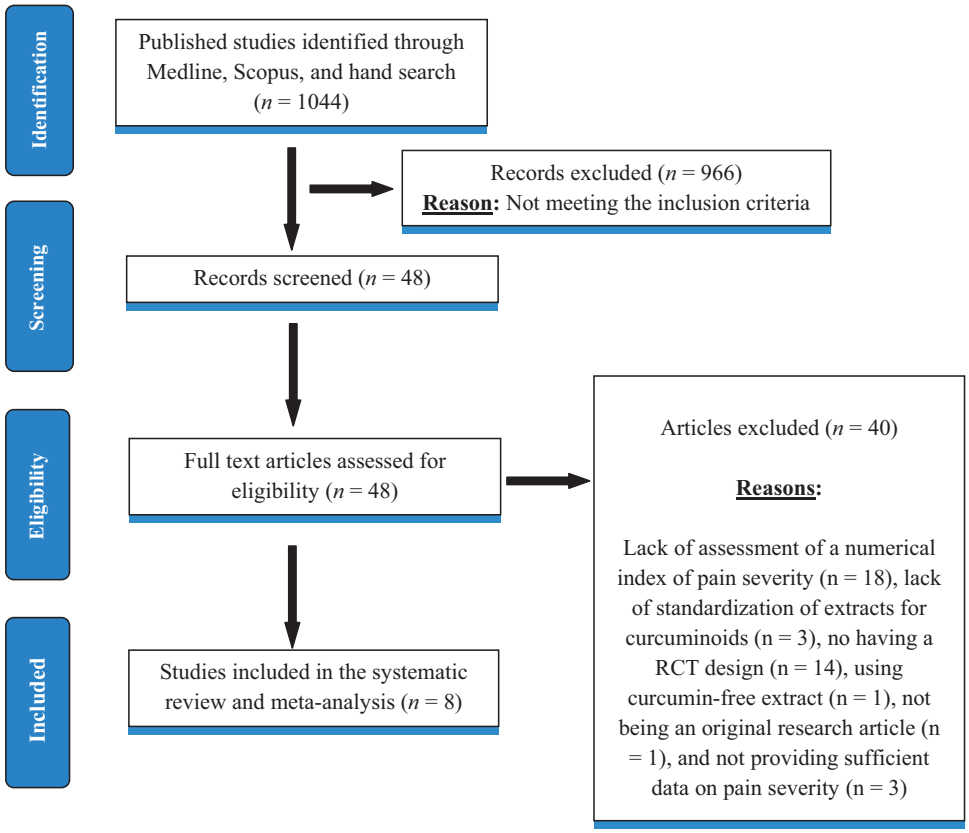

Figure 1 Flow diagram of the study selection procedure showing the number of eligible randomized controlled trials for the meta-analysis of the impact of curcuminoid supplementation on the severity of pain.

bioavailability of curcuminoids, absorption enhancement strategies were used in three studies by using a phytosomal delivery system [44], or co-administration of piperine [15,42], a well-known bioavailability enhancer [54,27]. Assessment of pain severity was performed using a graded VAS in six studies [15,26,32,35,42,44], McGill Pain Questionnaire-Short Form [41], or Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) [43].

Quantitative Data Synthesis

Efficacy on Pain

Meta-analysis of data from eight RCTs indicated a significant effect of curcuminoid supplementation in reducing pain severity (SMD: −0.57, 95% CI: −1.11 to −0.03, $P = 0.04$). Power analysis suggested a 100% statistical power for this comparison. The robustness of this effect was tested using a leave-one-out sensitivity analysis. It was found that the estimated pooled SMD was sensitive to the trials by Panahi et al. [15] and Kuptniratsaikul et al. [43]. Forest plots summarizing the impact of curcuminoids on pain severity are illustrated in Figure 2.

When the analyses were confined to the studies administering bioavailability-enhanced preparations of curcuminoids, a greater pooled effect size was found (SMD: −0.98, 95% CI: −1.81 to −0.15, $P = 0.02$) (Figure 3). Likewise, there was a greater effect in the subset of trials with a placebo control group (SMD: −0.88, 95% CI: −1.83 to 0.08, $P = 0.07$) compared to the subset with an active (NSAID) control group (SMD: −0.06, 95% CI: −0.27 to 0.15, $P = 0.57$). With respect to treatment duration, the reduction in pain severity did not reach statistical significance in either of the subset of trials lasting ≥ 6 weeks (SMD: −0.39, 95% CI: −1.02 to 0.24, $P = 0.23$) compared with the subset lasting < 6 weeks (SMD: −0.91, 95% CI: −2.29 to 0.46, $P = 0.19$); that is probably due to the small number of studies in each subset.

When the analysis was restricted to studies that used 100-point VAS for the assessment of pain severity, it was found that curcuminoid supplementation reduces pain by −19.33 points (95%CI: −29.80, −8.87; $P = 0.0003$) (expressed as weighted mean difference owing to the use of a similar measure).

Meta-Regression

Meta-regression analysis was conducted to evaluate the association between changes in pain severity and potential moderator variables. The impact of curcuminoids on pain severity was found to be independent of

Table 1 Demographic characteristics of the studies selected for analysis

		Agarwal (26)	Chandran and Goel (35)	Ryan (41)	Kuptniratsaikul, 2014 (43)	Drobnic (44)	Kuptniratsaikul, 2009 (32)	Durganprasad (42)	Panahi (15)
Ref		25	34	40	42	43	31	41	15
Jadad score		3	2	5	5	2	3	1	3
Year		2011	2012	2013	2014	2014	2009	2005	2014
Location		India	India	USA	Thailand	Spain	Thailand	India	Iran
Design		Randomized double-blind placebo-controlled parallel trial	Randomized single-blind active-controlled parallel trial	Randomized double-blind placebo-controlled parallel trial	Randomized single-blind active-controlled parallel trial	Randomized single-blind placebo-controlled parallel trial	Randomized single-blind active-controlled parallel trial	Randomized double-blind placebo-controlled parallel trial	Randomized double-blind placebo-controlled parallel trial
Duration of trial		2 weeks	8 weeks	7 weeks	4 weeks	4 days	6 weeks	6 weeks	6 weeks
Inclusion criteria		Patients undergoing laparoscopic cholecystectomy	Patients with active rheumatoid arthritis	Patients with breast cancer receiving radiotherapy	Patients with knee osteoarthritis	Patients with acute muscle injury induced by eccentric continuous exercise	Patients with knee osteoarthritis	Patients with tropical pancreatitis	Patients with knee osteoarthritis
Curcuminoid intervention		Pure curcuminoids (2,000 mg/day)	Pure curcuminoids (500 mg/day) plus sodium diclofenac (50 mg/day)	Pure curcuminoids (6,000 mg/day)	*Curcuma domestica* extract (1,500 mg/day) standardized as having 75–85% curcuminoids	Phytosomal curcumin (1,000 mg/day) equivalent to 200 mg/day curcuminoids	*Curcuma domestica* extract (2,000 mg/day) equivalent to 1,000 mg/day curcuminoids	Pure curcuminoids (1,500 mg/day) plus piperine (15 mg/day)	Pure curcuminoids (1,500 mg/day) plus piperine (15 mg/day)
Control intervention		Placebo	Sodium diclofenac (50 mg/day)	Placebo	Ibuprofen (1,200 mg/day)	Placebo	Ibuprofen (800 mg/day)	Placebo	Placebo
Participants	Case	25	15	14	171	9	45	8	19
	Control	25	15	16	160	10	46	7	21
Age (years)	Case	38.44 ± 12.8	47.00 ± 16.22	54.6 ± 12.3	60.3 ± 6.8	32.7 ± 12.3	61.4–8.7	23.6/12.8	57.32 ± 8.78
	Control	37.16 ± 12.7	48.87 ± 10.78	61.1 ± 11.2	60.9 ± 6.9	38.1 ± 11.1	60.0–8.4	27.8/16.8	57.57 ± 9.05
Male (%)	Case	20.0	26.7	0.0	8.2	100	21.2	87.5	26.3
	Control	16.0	6.7	0.0	13.1	100	18.2	100.0	19.0
BMI (kg/m^2)	Case	NS	22.73 ± 3.65	NS	26.5 ± 3.7	24.4 ± 1.0	26.4 ± 3.7	NS	28.75 ± 3.17
	Control	NS	21.99 ± 3.75	NS	26.6 ± 4.0	24.8 ± 1.7	26.8 ± 4.8	NS	29.64 ± 4.46
Diabetes (%)	Case	36.0	NS	NS	NS	NS	NS	50.0	NS
	Control	28.0	NS	NS	NS	NS	NS	25.0	NS
Hypertension (%)	Case	28.0	NS	NS	NS	NS	NS	NS	NS
	Control	20.0	NS	NS	NS	NS	NS	NS	NS
Duration of pain (months)	Case	NS	NS	NS	51.3 ± 53.4	NS	19.1 ± 19.6	12–36	NS
	Control	NS	NS	NS	52.0 ± 51.7	NS	22.3 ± 26.4	12–36	NS
Pain assessment tool		100-point VAS	100-point VAS	McGill Pain Questionnaire-Short Form	WOMAC	0–4 VAS	10-point VAS	10-cm VAS	100-point VAS

Values are expressed as mean ± SD or percentage. NS = not stated; BMI = body mass index; VAS = visual analog scale.

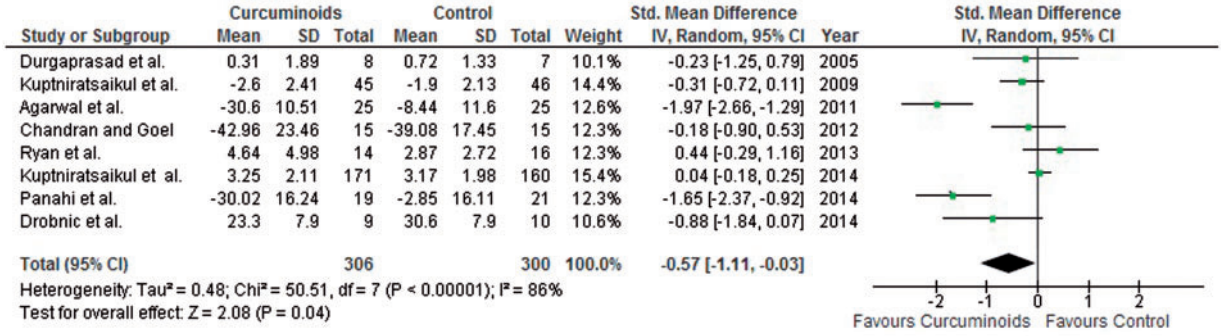

Figure 2 Forest plot detailing standardized mean difference and 95% confidence intervals for the impact of curcuminoid supplementation on the severity of pain.

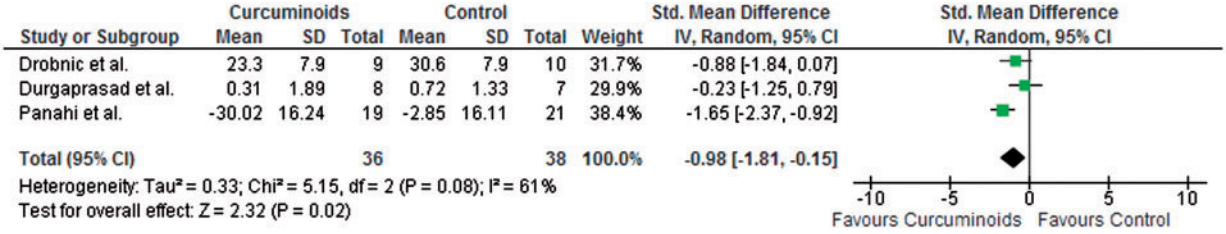

Figure 3 Forest plot detailing standardized mean difference and 95% confidence intervals for the impact of bioavailability-improved curcuminoids preparations on the severity of pain.

prescribed dose (slope: 0.00015; 95% CI: −0.00016 to 0.00046; $P = 0.348$) and duration of supplementation (slope: 0.168; 95% CI: −0.039 to 0.376; $P = 0.111$). Bubble plots of the meta-regression analyses are illustrated in Figure 4.

Publication Bias

Visual inspection of the funnel plot of the study precision (inverse SEM) by effect size (Hedges' *g*) suggested an asymmetry in the distribution of studies around the estimated pooled effect size. However, trim-and-fill analysis did not suggest any publication bias and no study was imputed. Funnel plot of the impact of curcuminoids on pain severity is illustrated in Figure 5.

Adverse Events

Among the eight included studies, adverse events were systematically recorded and assessed in six. Curcuminoids were reported to be safe and well-tolerated in all RCTs, and none of the studies reported a higher frequency of adverse events in the curcuminoid compared with the control group. Reported adverse events were gastrointestinal complications (nausea/vomiting, abdominal pain/distension, dyspepsia, and loose stool), fever, pitting edema, and throat infection. All these adverse events were reported to be mild, and none of them was responsible for withdrawal from the study. In two head-to-head comparison trials, most of the adverse events occurred less frequently in the curcuminoid group compared with sodium diclofenac [35] and ibuprofen [43] groups.

Pooled results displayed equivalent rates of total adverse events (RR: 0.84, 95% CI: 0.65, 1.07, $P = 0.154$) and drop-outs (RR: 0.87, 95% CI: 0.58, 1.31, $P = 0.515$) between curcuminoids and control treatment arms.

Discussion

Because low-quality studies with inappropriate controlling of treatment effects might bias the meta-analysis results, we decided to conduct a meta-analysis of RCTs with pre-specified criteria and exclude single-arm trials. We identified eight RCTs on the efficacy of curcuminoids for the management of pain. Altogether, these studies involved 606 patients, including 300 receiving curcuminoids. We found a SMD of −0.57 in favor of curcuminoids in comparison with placebo or conventional NSAIDS. This analgesic effect is clinically relevant on an individual patient basis, according to the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) consensus [55]. However, this analgesic effect was sensitive to some clinical trials with a high SMD [15,26,44]. We have not identified study particularities that could explain the high effect of curcuminoids in these studies. The referred studies

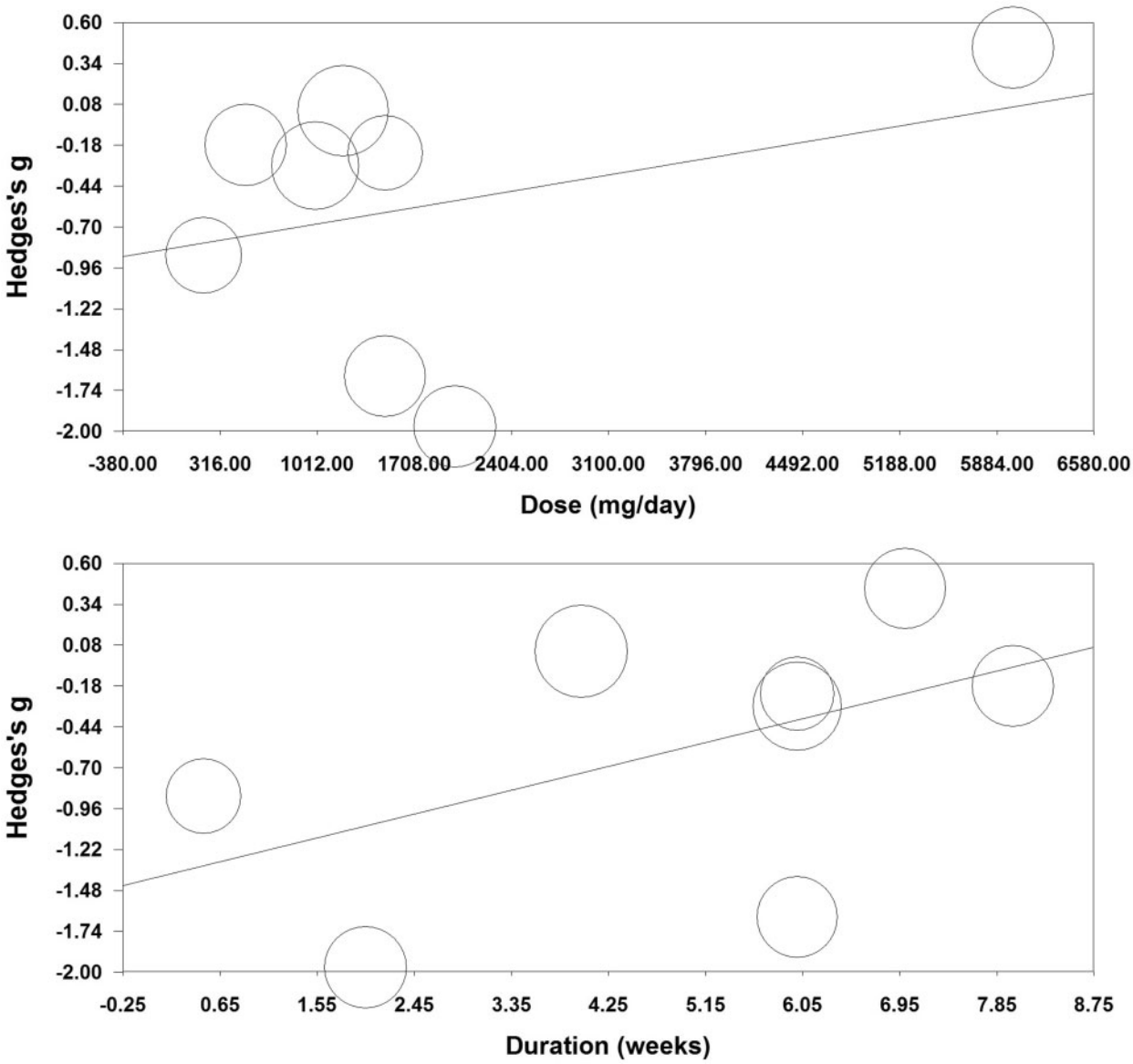

Figure 4 Mixed-effect meta-regression plots of the association between pain-relieving effects of curcuminoids and dose (left) and duration of supplementation (right). The size of each circle is inversely proportional to the variance of change.

investigated three different clinical conditions (muscle pain, osteoarthritis and postoperative pain) indicating that curcuminoids' effect is not associated with a particular painful condition. Further, these studies were not industry sponsored, a factor commonly reported to promote product efficacy.

We have also highlighted that the effect of curcuminoids on pain severity is independent of prescribed dose and duration of supplementation. This suggests that phase II trials investigating dose-escalade should be conducted to determine the optimal dose. We also suspect that the bioavailability of curcuminoids formulations used in the included studies remains a problem. The natural curcumin is poorly absorbed and rapidly metabolized in human limiting its clinical efficacy. The challenge is to increase its bioavaibility to reach plasmatic levels of curcumin corresponding to active concentration in vitro. In the included studies, three investigations used bioavailability-boosted products of curcuminoids by co-administration of piperine [15,42], or using phytosomal form of curcuminoids [44]. Hence, it may be speculated that the overall analgesic effect size of curcuminoids may be greater with bioavailability optimized preparations, a hypothesis that was confirmed by the results of subgroup analysis in the present study.

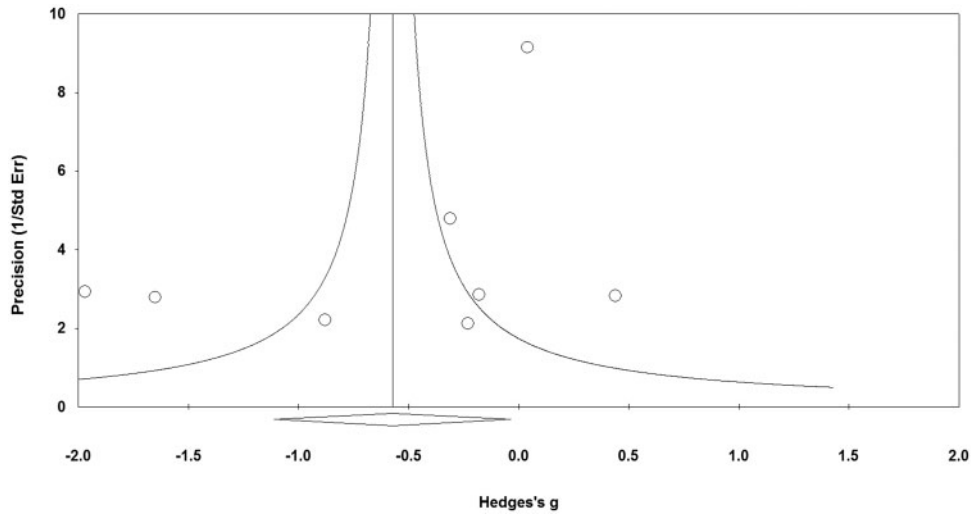

Figure 5 Funnel plots detailing publication bias in the studies selected for analysis.

Interestingly, two good quality studies reported that curcuminoids relieve pain in knee osteoarthritic patients [15,32]. Given the chronicity of pain in osteoarthritis and the common presence of gastro-intestinal and cardiovascular comorbidities, the benefits and risks of drugs given for this condition must be carefully weighed. In this context, curcuminoids, which show a favorable risk/benefits ratio, should be considered especially for the treatment of osteoarthritic patients with co-morbidities limiting the long-term and/or recurrent administration of drugs like oral NSAIDs and paracetamol. Compared with curcumin, NSAIDs and paracetamol had a lower effect size [31]. The majority of mild adverse effects reported were gastrointestinal disturbance (nausea/vomiting, abdominal pain/distension, dyspepsia, and loose stool). Further, the present meta-analysis shows that in studies comparing curcuminoids with NSAIDS (Ibuprofen or Diclofenac), curcuminoids exhibit less adverse effects than NSAIDS. Recently, a retrospective observational study summarizing the experience of 820 patients treated with a polysorbate supplemented curcuminoids extract for more than 6 months for various forms of painful osteoarthritis, reported that half of these patients were able to discontinue analgesic and anti-inflammatory drugs [31,56]. Clearly, these findings indicate that curcuminoids are safe and contribute to decrease the consumption of drugs with severe adverse effects.

Statistical analysis failed to demonstrate a bias in our meta-analysis. However, our meta-analysis is limited by the inherent potential for publication bias. Indeed, we included only published trials, and therefore we cannot fully exclude that some negative unpublished studies might have biased our results. Another limitation is that selected studies involved a small sample size, which may affect confidence in our conclusions. In addition, there was a considerable heterogeneity in the included trials in terms of the underlying painful condition. Although curcuminoids are multifunctional and multi-target compounds, further studies are still required to obtain a more precise effect size for each painful condition. Finally, there was not a substantial variation across the trials in terms of treatment dose and duration to allow a robust assessment of association between these parameters and treatment response. Therefore, future trials and patient-level pooled analyses are warranted to ascertain the association between pain-relieving effect of curcuminoids with dose and duration of supplementation.

In conclusion, this meta-analysis of RCTs with low risk of bias shows that curcuminoids supplements may be a safe and effective strategy to improve pain severity, by warranting further rigorously conducted studies to define the long-term efficacy and safety. Given the paucity of well-tolerated effective treatments and the well-known toxicity of NSAIDs, curcumin should be considered to alleviate pain in patients with chronic pain condition.

References

1 Sahebkar A. Are curcuminoids effective C-reactive protein-lowering agents in clinical practice? Evidence from a meta-analysis. Phytother Res 2014;28:633–42.

2 Panahi Y, Sahebkar A, Parvin S, Saadat A. A randomized controlled trial on the anti-inflammatory effects of curcumin in patients with chronic sulphur mustard-induced cutaneous complications. Ann Clin Biochem 2012;49:580–8.

3 Panahi Y, Sahebkar A, Amiri M, et al. Improvement of sulphur mustard-induced chronic pruritus, quality of life and antioxidant status by curcumin: Results of a randomised, double-blind, placebo-controlled trial. Br J Nutr 2012;108:1272–9.

4 Sahebkar A, Mohammadi A, Atabati A, et al. Curcuminoids modulate pro-oxidant–antioxidant

balance but not the immune response to heat shock protein 27 and oxidized LDL in obese individuals. Phytother Res 2013;27:1883–8.

5 Ono M, Higuchi T, Takeshima M, Chen C, Nakano S. Antiproliferative and apoptosis-inducing activity of curcumin against human gallbladder adenocarcinoma cells. Anticancer Res 2013; 33:1861–6.

6 Yoysungnoen-Chintana P, Bhattarakosol P, Patumraj S. Antitumor and antiangiogenic activities of curcumin in cervical cancer xenografts in nude mice. BioMed Res Int 2014; art. no. 817972.

7 Anand P, Nair HB, Sung B, et al. Design of curcumin-loaded PLGA nanoparticles formulation with enhanced cellular uptake, and increased bioactivity in vitro and superior bioavailability in vivo. Biochem Pharmacol 2010;79:330–8.

8 Henrotin Y, Clutterbuck AL, Allaway D, et al. Biological actions of curcumin on articular chondrocytes. Osteoarthritis Cartilage 2010;18:141–9.

9 Ramamoorthi G, Sivalingam N. Molecular mechanism of TGF-β signaling pathway in colon carcinogenesis and status of curcumin as chemopreventive strategy. Tumour Biol 2014;35:7295–305.

10 Zlotogorski A, Dayan A, Dayan D, et al. Nutraceuticals as new treatment approaches for oral cancer–I: Curcumin. Oral Oncol 2013;49:187–91.

11 Panahi Y, Saadat A, Beiraghdar F, Sahebkar A. Adjuvant therapy with bioavailability-boosted curcuminoids suppresses systemic inflammation and improves quality of life in patients with solid tumors: A randomized double-blind placebo-controlled trial. Phytother Res 2014;28:1461–7.

12 Panahi Y, Saadat A, Beiraghdar F, et al. Antioxidant effects of bioavailability-enhanced curcuminoids in patients with solid tumors: A randomized double-blind placebo-controlled trial. J Funct Foods 2014; 6:615–22.

13 Taylor RA, Leonard MC. Curcumin for inflammatory bowel disease: A review of human studies. Altern Med Rev 2011;16:152–6.

14 Panahi Y, Badeli R, Karami GR, Sahebkar A. Investigation of the efficacy of adjunctive therapy with bioavailability-boosted curcuminoids in major depressive disorder. Phytother Res 2015;29: 17–21.

15 Panahi Y, Rahimnia AR, Sharafi M, et al. Curcuminoid treatment for knee osteoarthritis: A randomized double-blind placebo-controlled trial. Phytother Res 2014;28:1625–31.

16 Nakagawa Y, Mukai S, Yamada S, et al. Short-term effects of highly-bioavailable curcumin for treating knee osteoarthritis: A randomized, double-blind, placebo-controlled prospective study. J Orthop Sci 2014;19:933–9.

17 Sahebkar A, Chew GT, Watts GF. Recent advances in pharmacotherapy for hypertriglyceridemia. Prog Lipid Res 2014;56:47–66.

18 Sahebkar A. Why it is necessary to translate curcumin into clinical practice for the prevention and treatment of metabolic syndrome? Biofactors 2013; 39:197–208.

19 Panahi Y, Khalili N, Hosseini MS, Abbasinazari M, Sahebkar A. Lipid-modifying effects of adjunctive therapy with curcuminoids-piperine combination in patients with metabolic syndrome: Results of a randomized controlled trial. Complement Ther Med 2014;22:851–7.

20 Panahi Y, Ghanei M, Hajhashemi A, Sahebkar A. Effects of curcuminoids-piperine combination on systemic oxidative stress, clinical symptoms and quality of life in subjects with chronic pulmonary complications due to sulfur mustard: A randomized controlled trial. J Diet Suppl 2016;13:93–105.

21 Panahi Y, Ghanei M, Bashiri S, Hajihashemi A, Sahebkar A. Short-term curcuminoids supplementation for chronic pulmonary complications due to sulfur mustard intoxication: Positive results of a randomized double-blind placebo-controlled trial. Drug Res 2014; DOI: 10.1055/s-0034-1389986.

22 Darvesh AS, Carroll RT, Bishayee A, et al. Curcumin and neurodegenerative diseases: A perspective. Expert Opin Investig Drugs 2012;21:1123–40.

23 Anand P, Kunnumakkara AB, Newman RA, Aggarwal BB. Bioavailability of curcumin: Problems and promises. Molecular Pharm 2007;4:807–18.

24 Cheng AL, Hsu CH, Lin JK, et al. Phase I clinical trial of curcumin, a chemopreventive agent, in patients with high-risk or pre-malignant lesions. Anticancer Res 2001;21:2895–900.

25 Ireson C, Orr S, Jones DJ, et al. Characterization of metabolites of the chemopreventive agent curcumin in human and rat hepatocytes and in rat in vivo, and evaluation of their ability to inhibit phorbol ester-induced prostaglandin E2 production. Cancer Res 2001;61:1058–64.

26 Agarwal KA, Tripathi CD, Agarwal BB, Saluja S. Efficacy of turmeric (curcumin) in pain and postoperative fatigue after laparoscopic cholecystectomy: A double-blind, randomized placebo-controlled study. Surg Endosc 2011;25:3805–10.

27 Shoba G, Joy D, Joseph T, et al. Influence of piperine on the pharmakinetics of curcumin in animals and human volunteers. Planta Med 1998;64:353–6.

28 Basnet P, Hussain H, Tho I, Skalko-Basnet N. Liposomal delivery system enhances anti-inflammatory properties of curcumin. J Pharma Sci 2012; 101:598–609.

29 Marczylo TH, Verschoyle RD, Cooke DN, et al. Comparison of systemic avaibility of curcumin with that of curcumin formulated with phosphatidylcholine. Cancer Chemother Pharmacol 2007;60:171–7.

30 Ohiri H, Yamakoshi H, Tomizawa M, et al. Synthesis and biological analysis of new curcumin analogues bearing an enhanced potential for the medicinal treatment of cancer. Mol Cancer Ther 2006;5:2563–71.

31 Henrotin Y, Priem F, Mobasheri A. Curcumin: A new paradigm and therapeutic opportunity for the treatment of osteoarthritis: Curcumin for osteoarthritis management. SpringerPlus 2013;2:9.

32 Kuptniratsaikul V, Thanakhumtorn S, Chinswangwatanakul P, Wattanamongkonsil L, Thamlikitkul V. Efficacy and safety of Curcuma domestica extracts in patients with knee osteoarthritis. J Altern Complement Med 2009;15:891–7.

33 Henrotin Y, Gharbi M, Dierckxsens Y, et al. Decrease of a specific biomarker of collagen degradation in osteoarthritis, Coll2-1, by treatment with highly bioavailable curcumin during an exploratory clinical trial. BMC Complement Altern Med 2014;14:159.

34 Appelboom T, MsciBiost CM. Flexofytol, a purified curcumin extract, in fibromyalgia and gout: A Retrospective Study. Open J Rheumatol Autoimmune Dis 2013;3:104–7.

35 Chandran B, Goel A. A randomized, pilot study to assess the efficacy and safety of curcumin in patients with active rheumatoid arthritis. Phytother Res 2012;26:1719–25.

36 Moini Zanjani T, Ameli H, Labibi F, Sedaghat K, Sabetkasaei M. The attenuation of pain behavior and serum cox-2 concentration by curcumin in a rat model of neuropathic pain. Korean J Pain 2014; 27:246–52.

37 Tajik H, Tamaddonfard E, Hamzeh-Gooshchi N. The effect of curcumin (active substance of turmeric) on the acetic acid-induced visceral nociception in rats. Pak J Biol Sci 2008;11:312–4.

38 Enyeart JA, Liu H, Enyeart JJ. Curcumin inhibits bTREK-1 K+ channels and stimulates cortisol secretion from adrenocortical cells. Biochem Biophys Res Commun 2008;370:623–8.

39 Jung KT, Lim KJ. Curcumin, COX-2, and Protein p300/CBP. Korean J Pain 2014;27:365–6.

40 Wei S, Xu H, Xia D, Zhao R. Curcumin attenuates the effects of transport stress on serum cortisol concentration, hippocampal NO production, and BDNF expression in the pig. Domest Anim Endocrinol 2010;39:231–9.

41 Ryan JL, Heckler CE, Ling M, et al. Curcumin for radiation dermatitis: A randomized, double-blind, placebo-controlled clinical trial of thirty breast cancer patients. Radiat Res 2013;180:34–43.

42 Durgaprasad S, Pai CG, Vasanthkumar, Alvres JF, Namitha S. A pilot study of the antioxidant effect of curcumin in tropical pancreatitis. Indian J Med Res 2005;122:315–8.

43 Kuptniratsaikul V, Dajpratham P, Taechaarpornkul W, et al. Efficacy and safety of *Curcuma domestica* extracts compared with ibuprofen in patients with knee osteoarthritis: A multicenter study. Clin Interv Aging 2014;9:451–8.

44 Drobnic F, Riera J, Appendino G, et al. Reduction of delayed onset muscle soreness by a novel curcumin delivery system (Meriva®): A randomised, placebo-controlled trial. J Int Soc Sports Nutr 2014; 11:31.

45 Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. Int J Surg 2010;8:336–41.

46 Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: Is blinding necessary? Control Clin Trials 1996; 17:1–12.

47 Borenstein M, Hedges L, Higgins J, Rothstein R. Comprehensive Meta-Analysis Version 2, Biostat, Englewood, NJ; 2005.

48 Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol 2005;5:art. no. 13.

49 Haenszel W, Hon NB. Statistical approaches to the study of cancer with particular reference to case registers. J Chronic Dis 1956;4:589–99.

50 Sahebkar A. Does PPARγ (2) Gene Pro12Ala polymorphism affect nonalcoholic fatty liver disease risk? Evidence from a meta-analysis. DNA Cell Biol 2013; 32:188–98.

51 Ferretti G, Bacchetti T, Sahebkar A. Effect of statin therapy on paraoxonase-1 status: A systematic review and meta-analysis of 25 clinical trials. Prog Lipid Res 2015 doi: 10.1016/j.plipres.2015.08.003.

52 Dupont WD, Plummer WD. Jr. Power and sample size calculations for studies involving linear regression. Control Clin Trials 1998;19:589–601.

53 Duval S, Tweedie R. Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics 2000; 56:455–63.

54 Atal CK, Dubey RK, Singh JJ. Biochemical basis of enhanced drug bioavailability by piperine: Evidence that piperine is a potent inhibitor of drug metabolism. Pharmacol Exp Ther 1985; 232:258–62.

55 Dworkin RH, Turk DC, Wyrwich KW, et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. J Pain 2008;9:105–21.

56 Appelboom T, Maes N, Albert A. A new curcuma extract (flexofytol®) in osteoarthritis: results from a belgian real-life experience. Open Rheumatol J 2014;8:77–81.