Efficacy of curcumin on inflammatory pain across different disorders: a systematic review and meta-analysis of Randomized controlled trials

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Abstract

Aim: to evaluate randomized controlled trials and perform a meta-analysis to assess the efficacy of curcumin on inflammatory pain in different disorders, in comparison to placebo and traditional pain treatments (NSAIDs and glucosamine plus chondroitin).

Method and design: meta-analysis of randomized controlled trials (RCT).

Data sources: Pubmed and Cochrane library were searched for relevant RCTs from January 1999 to July 2021. Reference lists were manually checked. Selection criteria: published RCTs comparing curcumin to placebo or other treatment modalities in adults with different pain disorders were eligible for inclusion.

Data collection and criteria: the studies were selected, and their quality was assessed by two review authors. Standardized mean difference (SMD) was used to analyze the continuous outcome using a random effect model.

Results: In all the 15 studies included 1475 subjects. Curcumin was found to be superior in controlling pain against placebo. Moreover, curcumin demonstrated a superior effect in controlling osteoarthritic pain when compared to Glucosamine and Chondroitin combination. However, Curcumin was found to be similarly effective to NSAIDs in controlling pain.

Conclusions: Curcumin was found superior in pain relief against placebo and combination of glucosamine and chondroitin. In addition, it demonstrated equal efficacy in relieving osteoarthritic pain, when compared to NSAIDs.

Key words: curcumin, inflammatory pain, osteoarthritis, NSAIDs, VAS, MOMAC, meta-analysis, Dysmenorrhea, post-surgical pain.

Abbreviation
VAS: Visual Analog Scale
WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.
NSAIDs: Non-Steroidal Anti-inflammatory Drugs

Introduction

Pain is defined as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage” (pain terms, 1979). The significance of chronic pain lies in the fact that it is one of the most common complaints presenting to the health care system. In a recent large scale study conducted by the World Health Organization across different countries, prevalence of pain was estimated to be 21.5% of the total visits in the primary health care setting (Gureje, O., Von Korff, M., Simon, G. E., & Gater, R., 1998). Moreover, prevalence of moderate to severe chronic pain among adults in Europe was estimated to be 19% (Breivik, H. et al. 2006). The effect of pain can be profound on quality of life, well-being, and pose an economic burden on the national health care systems. In Australia, a study showed that chronic pain was responsible for increased primary care visits, emergency visits, and hospitalization. In the UK, it is estimated that the annual cost of managing chronic pain is around £69 million/ year (Phillips C. J. ,2009). For these reasons pain is thoroughly investigated, and continuous search for safer and cheaper analgesics are always pursued.

Chronic Inflammatory pain is one of the types of pathological pain. It is caused by tissue injury which will produce neural plasticity, that involves both peripheral and central sensitization. The sensitization process leads to decreasing the nociceptive threshold, which consequently leads to patients experiencing spontaneous pain, hyperalgesia, and allodynia (Sun, J., et al 2018). The mechanism of inflammatory pain starts when tissue damage happens. This in turn, will result in the release of a group of chemical mediators, known as “the inflammatory soup”. These mediators will provoke nociceptors, which will produce pain. The mediators are Prostaglandins, TNFα, growth factors and kinins. When these mediators bind to nociceptive receptors, they start the process of peripheral sensitization. The binding activates protein kinase which will result in the reduction of the pain threshold leading to hyperalgesia (Mackey, S., 2004). Moreover, inflammatory mediators can stimulate central sensitization. They promote the expression of genes responsible for the production of COX-2 enzymes. These enzymes play an important role in the production of prostaglandins, which are important players in the inflammatory soup. One of the most important pharmacological agents that target this step are NSAIDS. They inhibit the COX-2 enzyme which will reduce the synthesis of prostaglandin. This will result in modulation of the inflammatory and nociceptive mediators, and reduction of inflammatory pain (Macky 2004). However, most of the traditional NSAIDs have a simultaneous effect on COX-1 enzyme. Inhibition of this enzyme is believed to be linked to major adverse events such as GI toxicity, increased bleeding time and risk of hemorrhage (Mackey, S. 2004). The potential adverse events can limit its use in the management of inflammatory pain in high-risk patients, therefore, the need for safer alternative has always been investigated. Herbal dietary derivatives such as curcumin have shown to have an anti-inflammatory effect and been thoroughly investigated (Yavarpour-Bali, Ghasemi-Kasman & Pirzadeh, 2019).

Turmeric is a herbal plant that has been widely consumed in southeast Asia, China and India for dietary and medicinal purposes (Wang et al., 2017). The main ingredients of turmeric are curcumin, demethoxycurcumin and bisdemethoxycurcumin (He et al., 2015), and curcumin longa is considered to the most valuable for therapeutic purposes. According to (Yavarpour-Bali, Ghasemi-Kasman & Pirzadeh, 2019), curcumin has proven to be pharmacologically beneficial, due to its antimicrobial, anti-inflammatory and antioxidant properties. Studies have proven that curcumin has an inhibitory effect on production of LPS-induced TNF-alpha and PGE2, which consequently has a positive effect on the inflammatory process and reduces inflammatory pain (Lantz, Chen, Solyom, Jolad & Timmermann, 2005). Moreover, the safety profile for curcumin has encouraged clinicians and researchers to extensively study curcumin as an alternative therapy for medical conditions (Dende et al., 2017). However, factors such as poor absorption, rapid metabolism, and elimination of curcumin in the human body posed major challenges in using curcumin as an alternative therapy (Siviero et al., 2015). It was not till recently, that new preparations of curcumin in labs have successfully enhanced its stability and bioavailability (Stanić, 2017). Nanotechnology implementations have successfully counteracted some of the curcumin innate behavior that usually hampers its therapeutic properties (Pichardo, E et al, 2020).

Several reviews have been conducted to investigate the effect of curcumin on Osteoarthritis. However, few reviews have investigated the effect of curcumin on chronic inflammatory pain in general. Therefore, this meta-analysis is aiming to investigate the effect of curcumin on pain associated with different inflammatory conditions (e.g., Rheumatoid Arthritis, Prostatitis, chronic inflammatory pelvic pain, post-operative pain) along with osteoarthritis.

Methods

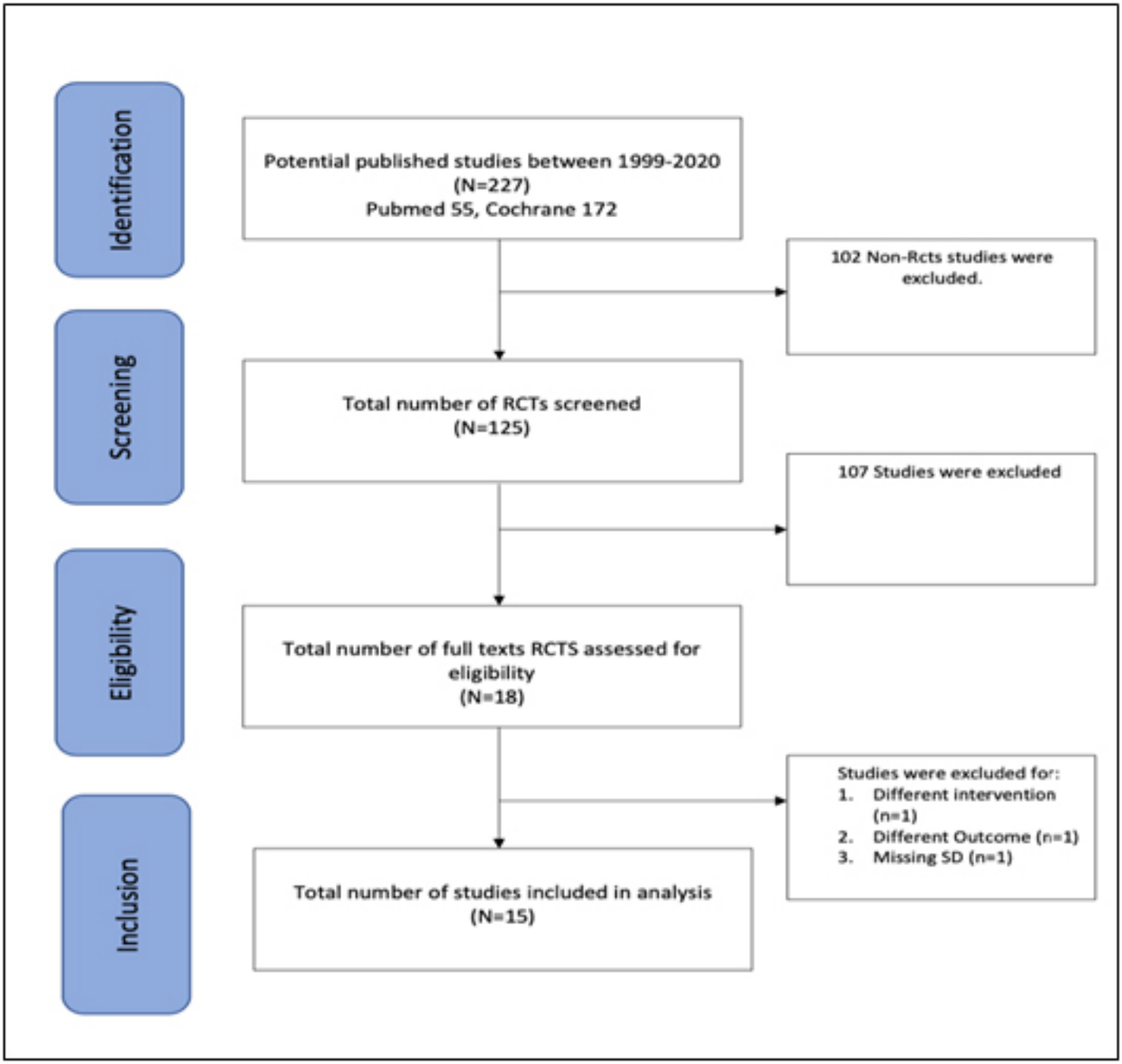
1. Search strategy

An electronic literature search was performed by two reviewers for RCTs assessing the effect of curcumin on inflammatory pain in different disorders. The electronic databases include Pubmed and Cochrane. Date was restricted to from January 1999 until July 2021. The following text terms were used, “curcumin”, “pain”, and “randomized controlled trials”. The reference list of all studies included were checked manually. The detailed retrieval process is shown in Figure 1.

2. Inclusion criteria

Inclusion criteria were: (1) Randomized control trials involving curcumin as the intervention, (2) control being NSAIDs, placebo or combination of Glucosamine plus Chondritin, (3) participants are adults, (4) RCTS assessing inflammatory pain and measuring numerical pain scales especially visual analogue scale (VAS) and WOMAC pain.

Figure 1: PRISMA chart of search strategy and study selection



3. Exclusion criteria

The exclusion criteria were: (1) using curcumin as an adjuvant therapy, (2) other type pf pain such as cancer pain and neurogenic pain. (3) non-randomized control trials. (4) different outcome. (5) studies missing valuable data to include in the meta-analysis such as standard deviation (Figure 1).

4. Data extraction

Three reviewers conducted the search and applied both the inclusion and the exclusion criteria. Data extraction from all studies was done separately. Later on, the data (characteristics, design and outcomes) were collected for final review among the 3 reviewers for final agreement to be included and analyzed.

5. Risk of bias and Quality assessment

The methodological quality of controlled trials was assessed using jaded scale, where points are given for three key methodological features of clinical trials, which are randomization, blinding and subjects follow up. An overall score of five is given. Studies with more than or equal to 3 points are considered high quality studies.

6. Statistical analysis

RevMan 5.1 was used for meta-analysis. The continuous variables were analyzed by standard Mean Difference (SMD) and 95% confidence interval (CI).

The chi-squared statistic and the I2 statistic were used for the assessment of heterogenicity. AP<0.05. I2>50% was considered as a significant heterogeneity. A random-effect model was used. A funnel plot was used to show publication bias. (Figure 3)

Three subgroup analyses were done to identify (1) effect of curcumin vs. Glucosamine and chondroitin, (2) Non-inferiority to NSAIDs, and (3) curcumin vs placebo.

Results

Table 1. included Study characteristics

Study	participants	Age mean Control	Age mean intervention	comparison	diagnosis	outcome	Jaded score
Chandran, 2012	45, mixed	48.87 (±10.78)	47.8 (±8.60)	Diclofenac	Rheumatoid arthritis	Disease activity score (pain)	5
Kuptniratsaikul H et al. 2009	107, mixed	60(±8.4)	61.4 (±8.7)	ibuprofen	Osteoarthritis	Pain on level walking numerical scale	5
Kuptniratsaikul et al. 2014	367, mixed	60.9 (±6.9)	60.3 (±6.8)	ibuprofen	Osteoarthritis	WOMAC pain	5
Belcaro H et al. 2014	124, mixed	56.6 (±4.7)	55.8(±5.8)	Glucosamine +chondroitin	Osteoarthritis	WOMAC pain	2
Haroyan et al. 2018	201, mixed	54.65 (±8.84)	56.04(±8.55)	placebo	Osteoarthritis	WOMAC pain	5
Khanna et al. 2020	80, mixed	53.4 (±6.64)	51.5 (±5.95)	Glucosamine +chondroitin	Osteoarthritis	Visual analogue scale	5
Madhu et al. 2013	120, mixed	56.77 (±9.98)	56.63(±10.58)	placebo	Osteoarthritis	Visual analogue scale	5
Madhu et al. 2013	120, mixed	56.8 (±7.99)	56.63(±10.58)	Glucosamine	Osteoarthritis	Visual analogue scale	5
Morgia et al. 2017	55, mixed	Median 32 (IQ 29-38)	Median 32 (IQ 28.75-38.75)	placebo	Chronic prostatitis/ chronic pelvic pain syndrome type 3	Visual analogue scale	3
Panahi H et al. 2014	40, mixed	57.57 (±9.05)	57.32(±8.78)	placebo	Osteoarthritis	WOMAC pain	5
Thomas et al. 2020	72, mixed	52.3 (±4.59)	51.7 (±5.52)	Glucosamine +chondroitin	Osteoarthritis	Visual analogue scale	3
Moharamzad et al, 2011	67, mixed	unavailable	unavailable	placebo	Osteoarthritis	Visual analogue scale	5
Srivastava et al, 2016	133, mixed	50.27 (±8,63)	50.23(±8.08)	placebo	Osteoarthritis	Visual analogue score	5
Nakagawa et al, 2014	41, mixed	66.2 (±7.2)	71.9(±5.3)	placebo	Osteoarthritis	Visual analogue scale	5
Agarwal et al, 2011	50, mixed	37.16 (±12.7)	38.44(±12.8)	placebo	Post laparoscopic cholecystectomy	Visual analogue scale	5
Tabari et al, 2020	74, females	Range 18-35	Range 18-35	placebo	dysmenorrhea	Visual analogue scale	5

Results

1. Study selection

Included studies were selected after going through the process of identification, screening, eligibility and inclusion. The flow process is shown in Figure 1. Using search terms mentioned above, 227 articles were found in Cochrane and PubMed. A total of 125 potential randomized controlled trials studies were identified. Exclusion criteria was applied and a total of 15 studies were included in the analysis.

2. Study and patient characteristics

Table 1 shows the details of study characteristics of all 15 suitable studies included in the meta-analysis. The number of total participants is 1,475, and the scale of each RCT was 40-367. All of the studies were published between 2009 and 2020.

Table 2. Description of Jaded score assessment

Study	Year	Randomization	Blinding	Follow-up of patients	Total jaded score
Chandran et al.	2012	2/2	2/2	1/1	5/5
Kuptniratsaikul H et al.	2014	2/2	2/2	1/1	5/5
Kuptniratsaikul et al.	2009	2/2	2/2	1/1	5/5
Belcaro H et al.	2014	1/2	0/2	1/1	2/5
Haroyan et al.	2018	2/2	2/2	1/1	5/5
Khanna et al.	2020	2/2	2/2	1/1	5/5
Madhu et al.	2013	2/2	2/2	1/1	5/5
Morgia et al.	2017	1/2	1/2	1/1	3/5
Panahi H et al.	2014	2/2	2/2	1/1	5/5
Thomas et al.	2021	2/2	0/2	1/1	3/5
Moharamzad et al.	2011	2/2	2/2	1/1	5/5
Srivastava et al.	2016	2/2	2/2	1/1	5/5
Nakagawa et al.	2014	2/2	2/2	1/1	5/5
Tabari et al.	2020	2/2	2/2	1/1	5/5
Agarwal et al.	2011	2/2	2/2	1/1	5/5

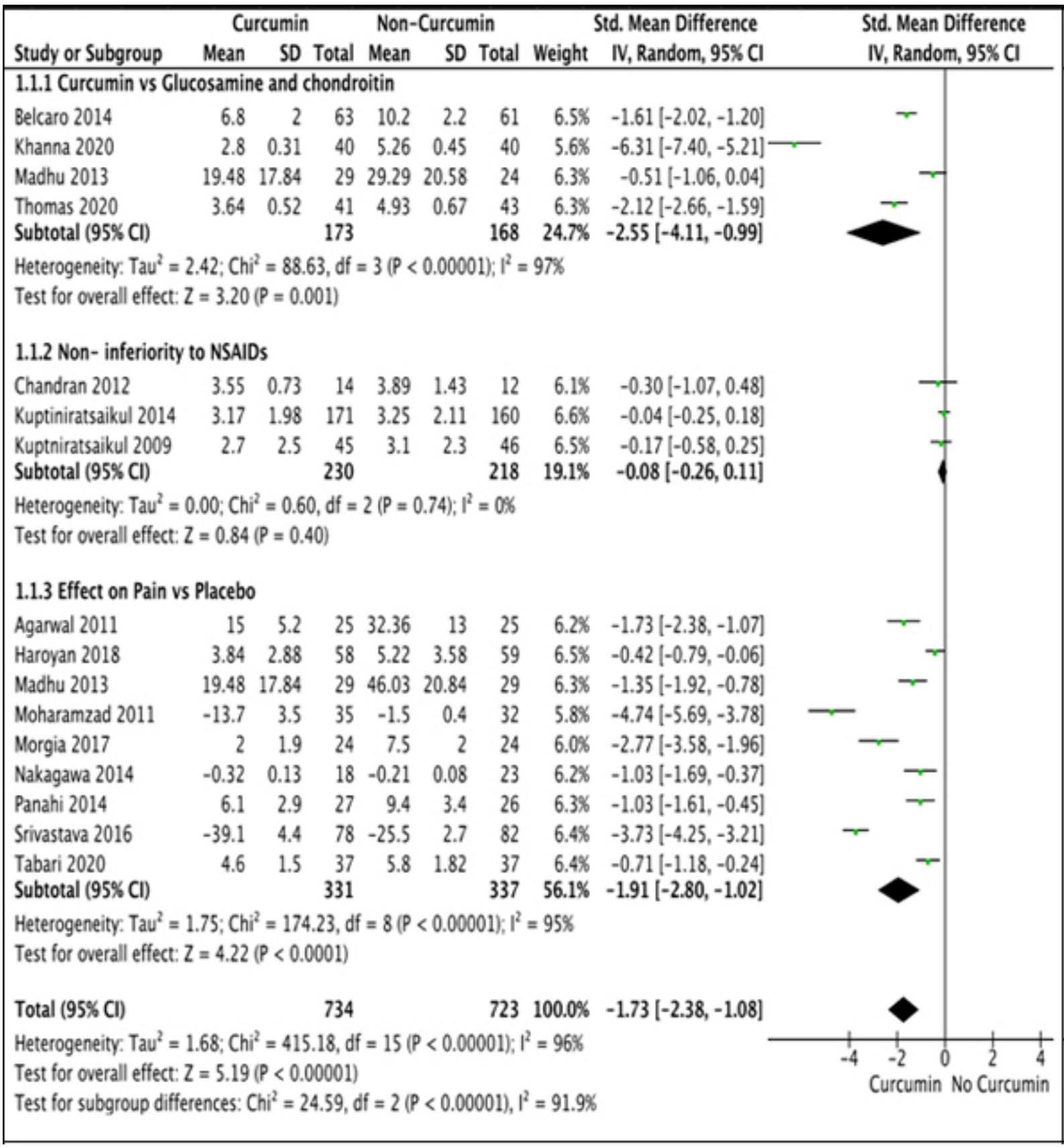
Fifteen studies were included in this meta-analysis. A total number of 1,457 subjects were included, 723 in control and 734 in intervention. Most of the studies were high quality studies and one only was of low quality.

Subgroup analysis was done. In assessing effect of curcumin vs the combination of Glucosamine plus chondroitin, four studies showed that there was significant difference between groups (SMD=-2.55, 95 % CI (-4.11,-0.99), P 0.74). Assessment of heterogeneity was done through chi square test and I2 showing high heterogeneity. Chi2=88.63, df=3, p<0.00001, and I2=97% (Figure 3).

In assessing effect of curcumin vs. NSAIDs, three studies showed that there was no significant difference between groups (SMD=-0.08, 95 % CI (-0.26, 0.11), P 0.40). Assessment of heterogeneity was done through chi square test and I2 showing low heterogeneity. Chi2=0.60, df=2, p=0.74, and I2=0%. (Figure 2).

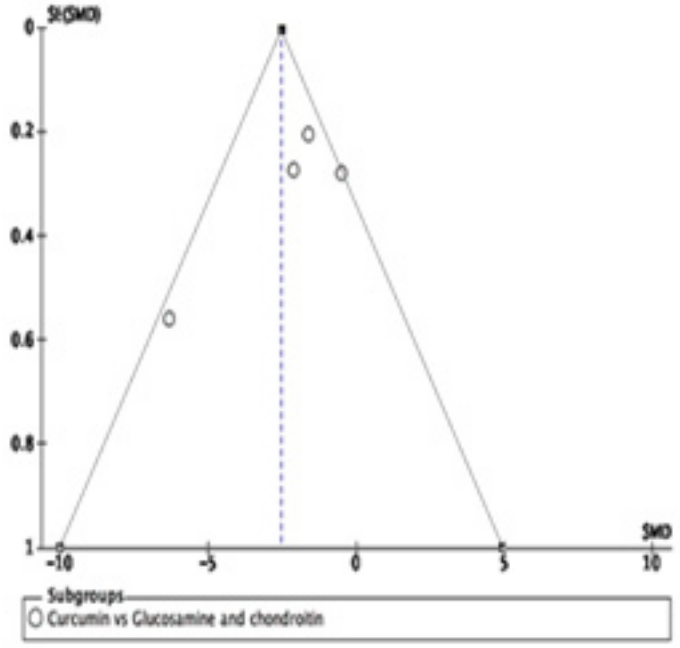
In assessing effect of curcumin vs. placebo, nine studies were included, and analysis showed significant difference between groups (SMD=-1.91, 95 % CI (-2.80, -1.02), P <0.0001). Assessment of heterogeneity was done through chi square test and I2 showing high heterogeneity. Chi2=174.23, df=8, p <0.00001, and I2=95%. (Figure 2).

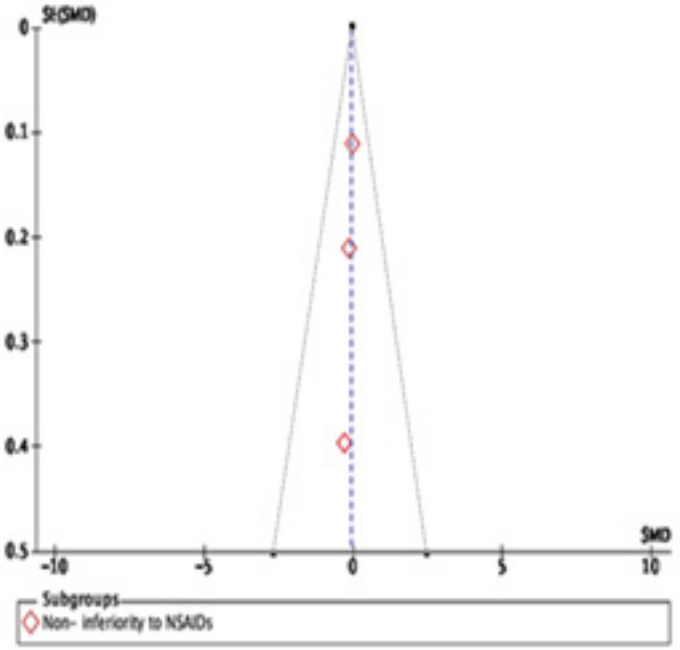
Figure 2: Forest plot.

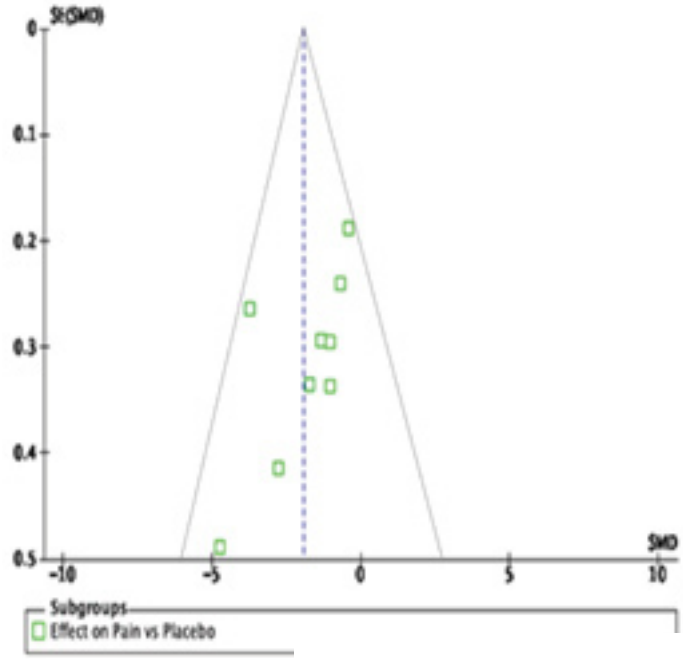


Publication Bias assessment:

Funnel plot was produced to assess the publication bias in every sub-group analysis, which indicated that there is no publication bias (Figure 3).







Discussion

The aim of our meta-analysis was to assess the effect of curcumin on different medical conditions presenting with chronic inflammatory pain (osteoarthritis, Rheumatoid arthritis, chronic pelvic pain type 3, prostatitis, dysmenorrhea and Post-operative pain). Curcumin has demonstrated a superior effect on pain control against placebo in osteoarthritis, rheumatoid arthritis, post-surgical pain and dysmenorrhea. In addition, subgroup analysis was conducted to investigate the effect of curcumin against traditionally used medications (NSAIDS and combination of glucosamine and chondroitin). Results drawn from 3 RCTs showed that curcumin is non-inferior to NSAIDs in alleviating osteoarthritic pain. Moreover, curcumin has demonstrated a superior effect in alleviating osteoarthritic pain when compared to glucosamine plus chondroitin in four RCTS.

The overall effect of curcumin on alleviating pain secondary to osteoarthritic changes supports previous published reviews. However, our meta-analysis has included different conditions that manifest inflammatory pain, such as dysmenorrhea, rheumatoid arthritis, post-operative pain, prostatitis and chronic pelvic pain, which has proven to be effective.

Most of the RCTs included are conducted on Asian populations. This is secondary to the fact that curcumin has been widely used for its dietary and medicinal purposes in the Asian culture. This could limit the generalizability of the results to other ethnic groups.

Strengths and limitation

The meta-analysis included 15 well conducted RCTs, most of them of high quality (achieved score of five on Jaded score). Moreover, the total number of participants included in the analysis is 1,457. The curcumin preparation in the RCTs was appropriate and increases the bioavailability and absorption for the participants. Finally, in comparison to previously published reviews, this analysis included wider variety of inflammatory conditions that could present as pain.

On the other hand, most studies were conducted in Asia and comprised of Asian populations, which limits the use of these results on different ethnic groups. The meta-analysis did not take into consideration the time duration of treatment, dose factors and different conditions. The difference in the duration of treatment in the RCTs, doses, preparation can explain the increased heterogeneity in the results. Finally, the meta-analysis did not investigate the adverse events of curcumin and its safety profile in the RCTs.

Future research can be done to investigate the effect of curcumin on pain in different ethnic groups to solidify the generalizability of these findings.

Conclusion

In this analysis, curcumin was found superior in pain relief against placebo and combination of glucosamine and chondroitin. In addition, it demonstrated equal efficacy in relieving osteoarthritic pain, when compared to NSAIDs. It also showed excellent safety profile in previous literature.

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