A Systematic Review of the Clinical Use of Curcumin for the Treatment of Osteoarthritis

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Abstract

Osteoarthritis is characterized by degeneration of joint structure over time, resulting in limitation of joint mobility. There is growing evidence that curcumin has anti-inflammatory properties and could be a potential therapeutic option for chronic inflammatory diseases. Hence, curcumin could potentially have a positive impact on osteoarthritis symptoms. This systematic review aimed to estimate the effects of curcumin on osteoarthritis. We systematically searched PubMed, ISI, Scopus, and Google Scholar up to March 4, 2020 to identify randomized controlled trials that evaluated the effects of consumption of all types of curcumin compounds in the treatment of osteoarthritis, especially in patients with knee osteoarthritis. Seventeen trials were identified. The duration of the included studies varied from 4 weeks to 8 months. Across all trials, 13 studies involved screening using Western Ontario and McMaster Universities (WOMAC) scores and 11 studies used visual analog scales (VAS) for recording pain from baseline to post-intervention. There was a significant improvement in VAS and overall WOMAC scores with oral administration of various types of curcumin formulations with no severe adverse effects. In conclusion, different types of curcumin compounds may be beneficial as an alternative or complementary agent for the management of osteoarthritis. Moreover, certain curcumin compounds with higher bioavailability tended to show more positive effects.

Keywords

Osteoarthritis · Arthritis · Curcumin · WOMAC · Systematic review

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16.1 Introduction

Osteoarthritis is one of the most common types of arthritis and is characterized by degeneration of the joint structure [1]. This condition exacerbates over time and has been associated with knee pain and the progression of cartilage degeneration and leading to chronic disability [2]. The prevalence of osteoarthritis is increasing even in early age groups, resulting in considerable morbidity and a significant economic burden [3, 4]. Studies have shown that although the role of aging in the pathogenesis of osteoarthritis is significant, there are other underlying mechanisms that contribute to osteoarthritis [5, 6]. An increasing number of studies have shown that the release of inflammatory cytokines in OA activates several molecular pathways involved in the dysregulated metabolism of chondrocytes, the cells involved in cartilage formation and maintenance [7].

One of the main treatment strategies for pain relief and functional improvement in knee osteoarthritis is the use of anti-inflammatory drugs such as non-steroidal anti-inflammatory agents (NSAIDs), although these have some gastrointestinal side effects [8]. There is growing evidence that nutraceuticals as well as medicinal plants could potentially act as a complementary therapy for the management of many chronic inflammatory conditions to reduce the safety risks and side effects associated with NSAIDs [9–14]. Curcumin, commonly called diferuloylmethane, is a hydrophobic polyphenol derived from the rhizome of *Curcuma longa* (the culinary spice plant), which has a multitude of biological and pharmacological effects [15–20]. Furthermore, curcumin has been used as a health-promoting agent for many ailments due to its properties [21–25]. Biochemically, the curcuminoid compounds include curcumin, dimethoxy curcumin (DMC), bisdemethoxycurcumin (BDMC), and keto-enol tautomers [26]. In vivo and in vitro studies have suggested that curcuminoid formulations may have anti-apoptotic effects and inhibit or slow the catabolic actions of key inflammatory mediators in the early stages of the disease [27–31]. Also, it has been reported that they scavenge reactive oxygen and nitrogen species and may block inflammatory pathways that have been associated with the progression of knee osteoarthritis [29].

Several clinical trial studies have now been conducted to evaluate the effect of curcuminoids on osteoarthritis [32]. Although a recently conducted meta-analysis concluded that curcuminoid formulations could be potentially beneficial for OA patients, the sample size (5 studies) was not adequate and had significant heterogeneity. In addition, publication bias was not assessed. To our knowledge, there is no comprehensive review assessing the effectiveness of different curcumin compounds in the management of OA. Therefore, the aim of this study was to systematically review and summarize the anti-osteoarthritic effects of various curcumin compounds utilizing published randomized controlled trial (RCT) data in adults.

16.2 Materials and Methods

16.2.1 Eligibility Criteria

This study reviewed evidence from RCTs of children, adults, and older people that evaluated the effects of all types of curcumin compounds in the management of osteoarthritis, especially in knee osteoarthritis patients. As the main outcome, the therapeutic effect of curcumin was measured using the improvement of Western Ontario and McMaster Universities (WOMAC) scores and visual analog scales (VAS). As a secondary outcome, evaluation of changes in other pains and performance, as well as knee injury questionnaires has been considered. Additionally, any reports or data in selected studies on improvement in inflammatory biomarkers and adverse have been included.

16.2.2 Search Strategy

We conducted a systematic review of the literature according to the PRISMA guidelines in order to answer our objectives. A comprehensive search was performed on March 4, 2020, in

which we searched the PubMed, ISI, Scopus, and Google Scholar databases, using keywords related to osteoarthritis and *Curcuma longa* without time restrictions. Only English articles were included. The following keywords were used in searches of all the databases: "curcumin" OR "curcuminoids" OR "Curcuma domestica" OR "Curcuma Longa" OR "curcuma" OR "turmeric" AND "osteoarthritis" OR "arthritis." Whenever possible, Medical Subject Headings (MESH) terms were used. Finally, a search was performed on the reference lists of the included original papers and review articles to identify other relevant works for inclusion.

16.2.3 Selection of Studies

RCTs were included that evaluated the effects of different types of curcumin and curcumin complexes in patients with osteoarthritis, in comparison to placebo or to patients who used standard analgesics treatments such as diclofenac, glucosamine, and ibuprofen. Studies with related titles were then collected and screened. Studies found in more than one database were excluded. After this, full paper manuscripts were studied, and irrelevant publications were removed.

16.2.4 Data Extraction

Relevant information was extracted from selected studies which included the following: (1) study design; (2) patient characteristics; (3) intervention regimens; (4) controls (placebo or standard treatment) regimens; (5) safety and adverse effects from treatment; and (6) changes in inflammatory marker levels if they reported. The main outcome of concern was the treatment efficacy of curcumin complex, classified as improvements in WOMAC or VAS scores, compared to the control groups.

16.2.5 Quality Assessment of Studies

The Jadad scale was used to assess the quality of the included studies. This scale considers the following items: randomization (0–2 points), blinding (0–2 points), and dropouts and withdrawals (0–1 point). According to this scale, the overall score of a study ranges between 0 and 5, with higher scores indicative of better quality [33]. Studies with Jadad scores of ≤ 2 and ≥ 3 were considered as low and high quality, respectively [34].

16.3 Results

16.3.1 Search Results

A total of 1251 studies were selected during the initial search, of which 817 were not duplicates. After reading the titles and abstracts, 784 references were omitted after which 33 articles remained. Full texts of these 33 articles were reviewed and 16 articles were omitted due to duplication of data ($n = 3$); curcumin was administrated in combination with other substances ($n = 9$); the source was a conference report ($n = 2$); the source was a study protocol ($n = 1$); or it was a non-English language article ($n = 1$). All included studies were RCTs. The results of the search are shown in Fig. 16.1.

16.3.2 Study Characteristics

The main characteristics of the trials included in this systematic review are summarized in Table 16.1. The total number of participants enrolled in the included studies was 1758, with sample sizes ranging from 25 to 367 participants and a mean age ranging from 38 to 80 years. Three studies reported different outcomes with the same population [35–37]. The most majority of studies were conducted on Asian populations and one study was from Belgium [38]. Follow-up analyses ranged from 4 weeks to 8 months. The treatment formulation assigned to the patients included lipid-based curcumin, curcuminoids, enhanced curcumin, and *Curcuma longa* extracts. The dosage of supplemental curcumin or lipid-based curcumin ranged from 40 mg to 200 mg per day [40–44]. Five studies used *Curcuma*

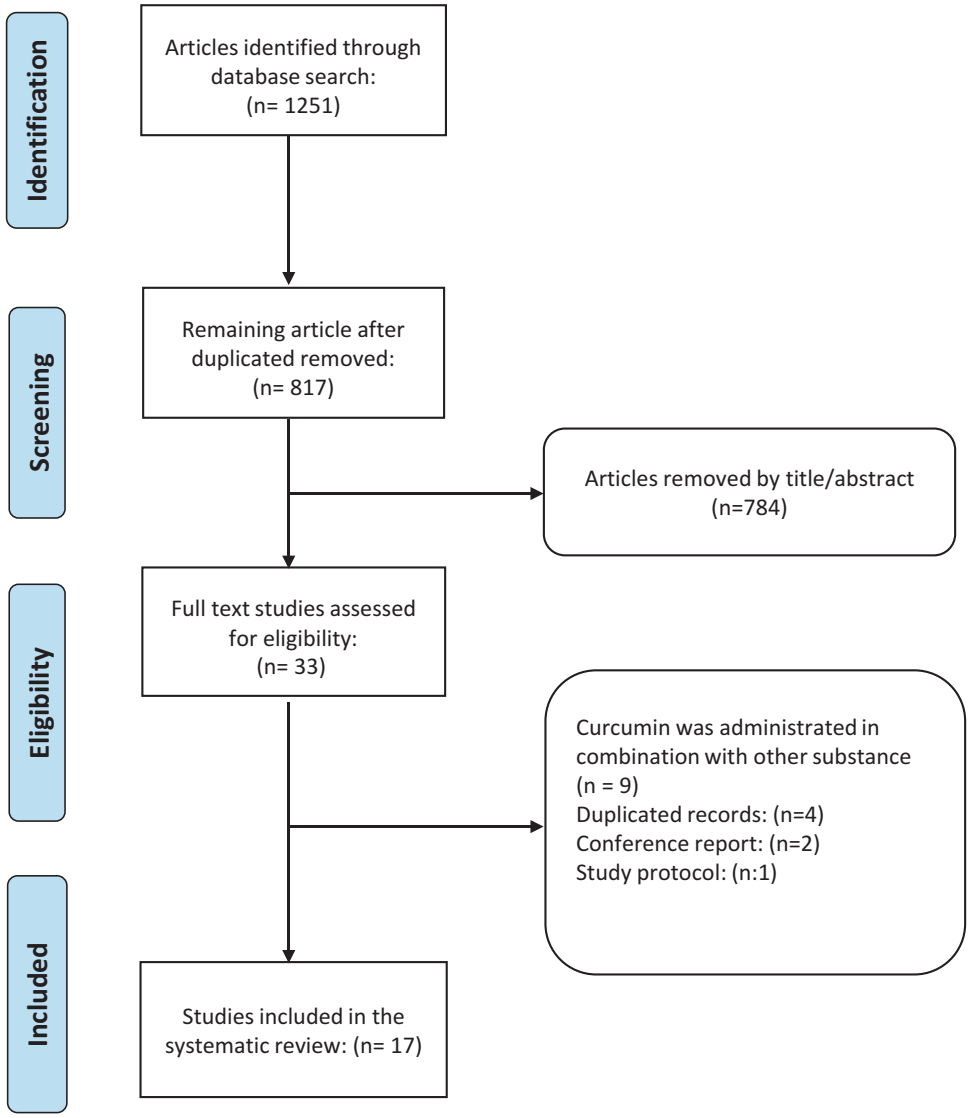

Fig. 16.1 Flow chart of the study selection process

longa extract supplements with a dose range of 0.5–1 g [38, 44–47]. Seven studies used pure curcumin at different dosages ranging from 0.5 to 2.5 g curcuminoids [35–37, 48–50]. Among the 17 randomized clinical trials, 12 compared the effectiveness of curcumin with placebo, two studies were a comparison with the usual treatments [39, 40], two compared curcumin with NSAIDs [44, 49], and one had no control group but had two intervention groups (curcumin, curcumin plus exercise) [51].v

16.3.3 WOMAC and VAS Outcomes

The main outcome for 11 out of 15 studies [35–37] was the WOMAC index [35, 39–42, 44–47, 50, 51], while 7 studies also measured components of the WOMAC assessment, including pain sensation, joint stiffness, and physical function [35, 39, 40, 44, 46, 47, 50]. In addition, the VAS tool was used by 10 studies to measure amounts of pain [35, 38, 41, 43, 45–49, 51]. Three studies also used the global Knee injury and Osteoarthritis

Table 16.1 Summary of the studies included in the systematic review (arranged alphabetically by first author's last name)

Author, year, country	Size	Inclusion criteria	Age Range (years) or mean	Study design	Intervention	Control	Duration	Main results	Jadad score
Belcaro et al. (2010), Italy [39]	100	Criteria for primary knee osteoarthritis (OA) (grade 1 or 2) according to American Rheumatism Association	In: 43.6 ± 5.5/ Co: 44.2 ± 6	Trial	Usual treatment+ Meriva (curcumin-phosphatidylcholine complex): Two 500-mg tablets daily, (1000 mg/day, corresponding to 200 mg curcumin/ day)	No placebo- only usual treatment	8 months	(1) Pain sensation, joint stiffness, and physical function improved significantly with Meriva, using Western Ontario and McMaster Universities (WOMAC) scores (pain, stiffness, and physical function were all positively affected by treatment) (2) Meriva significantly improved the Karnofsky Scale (from 73.3 at inclusion to 92.2 at study completion), with no significant improvements in controls (3) A significant improvement of mobility, evaluated by a treadmill was found in the intervention compared with the control group (4) sCD40L, IL-1β, IL-6, sVCAM-1, and ESR significantly decreased in the intervention group with no changes in the control group	1

(continued)

Table 16.1 (continued)

Author, year, country	Size	Inclusion criteria	Age Range (years) or mean	Study design	Intervention	Control	Duration	Main results	Jadad score
Belcaro et al. (2010), Italy [39]	50	Knee OA patients confirmed by X-ray	In: 44.4 ± 7.2/ Co: 45.3 ± 8.6	Trial	Usual treatment + Curcumin with soy phosphatidylcholine (Meriva®, Indena SpA) (200 mg curcumin)	No placebo- only usual treatment	3 months	In the treatment compared to the control group: (1) The global WOMAC score significantly decreased by 58% (pain, stiffness, and physical function were all positively affected by treatment) (2) Walking distance in the treadmill test was significantly prolonged (3) CRP levels decreased in the subpopulation with high CRP (4) Treatment costs (use of anti-inflammatory drugs, treatment, and hospitalization) were reduced significantly in the treatment group	0
Gupte et al. (2019), India [41]	50	Knee OA as confirmed by the American College of Rheumatology (ACR) criteria like knee pain, stiffness/ crepitus and osteophytes in X-ray	In: 57 ± 7.5/ Co: 54 ± 8	RCT	Solid lipid curcumin particles (SLCP) (400 mg twice daily delivering 80 mg of curcumin per capsule) or Ibuprofen with the placebo group (400 mg each once daily)	Capsule Ibuprofen (400 mg) + placebo capsule (dextrin)	90 days	(1) The WOMAC and visual analog scale (VAS) score significantly decreased in both groups compared to baseline. There was no significant difference between both the groups (2) No difference between the groups was found regarding inflammatory markers differences (3) Levels of urine CTX-II were maintained in both groups (4) There were no serious adverse events reported in both groups	3

Haroyan et al. (2018), Armenia [50]	210	Degenerative hypertrophic knee OA (M 17, according to International Statistical Classification of Diseases and Related Health Problems tenth Revision (ICD-10) version for 2014 of bone joints and verified by Radiography)	56.2	RCT	CuraMed® 500 mg capsules (333 mg curcuminoids) and Curamin® 500 mg capsules (350 mg curcuminoids and 150 mg boswellic acid) taken orally three times	Placebo	12 weeks	(1) A significant effect of Curamin® (curcuminoids and 150 mg boswellic acid) compared to placebo in physical performance tests and the WOMAC total and joint pain scores (2) Superior efficacy of CuraMed (curcuminoids) vs placebo was observed only in physical performance tests (3) No difference was found between groups regarding the WOMAC stiffness index (4) The effect size compared to placebo was comparable for both treatment groups but was superior in the Curamin® group (5) The treatments were well tolerated	5
Hashemzadeh et al. (2019), Iran [42]	71	Knee OA patients[a]	[a]	RCT	40 mg nanocurcumin capsule every 12 h	Placebo	6 weeks	A significant decrease was observed in the overall score, along with the scores of pain, stiffness, and physical activity subscales of the WOMAC questionnaire in patients of the nanocurcumin group compared with the placebo group	-[a]

(continued)

Table 16.1 (continued)

Author, year, country	Size	Inclusion criteria	Age Range (years) or mean	Study design	Intervention	Control	Duration	Main results	Jadad score
Henrotin et al. (2019), Belgium [38]	150	Femorotibial and/or femoropatellar symptomatic knee OA diagnosed according to the clinical and radiological criteria of ACR	(A) 60.9 ± 9.78 (B) 61.4 ± 7.49 (C) 63.3 ± 7.69	RCT	(A) Bio-optimized *Curcuma longa* extracts (BCL) low dosage 2 × 2 caps/day plus placebo 2 × 1 cap/day (B) BCL high dosage 2 × 3 caps/day (each capsule contained 46.67 mg of turmeric rhizome extract (*Curcuma longa* L.), polysorbate 80 [E433] as an emulsifier, and citric acid [E330] as an acidity regulator)	(C) Placebo 2 × 3 capsules /day Placebo (sunflower seed oil)	3 months	(1) Low and high doses of BCL showed a greater decrease of Patient Global Assessment of Disease Activity (PGADA) than placebo (2) Pain (VAS) reduction at day 90 in low- and high-dose BCL groups was significantly higher than that in the placebo (3) Global Knee injury and Osteoarthritis Outcome Score (KOOS) significantly decreased over time, but changes did not significant across treatment arms (4) The ratio of patients with adverse events related to the product was similar in the placebo and treatment groups	5
Kuptniratsaikul et al. (2014), Thailand [44]	367	Knee OA patients according to the American Rheumatism Association criteria who had a numerical rating scale of knee pain of ≥5 out of 10	Curcumin: 60.3 ± 6.8/ Ibuprofen: 60.9 ± 6.9	RCT	*Curcuma domestica* extracts 1500 mg/day	Ibuprofen 1200 mg/day	4 weeks	(1) The mean of all WOMAC scores (total and sub-total scores for pain, stiffness and physical function) showed significant improvement when compared with the baseline in both groups but there were no differences between groups (2) The side effect profile was similar but with fewer gastrointestinal adverse event reports in the *C. domestica* extract group	5

Madhu et al. (2013), India [45]	120	Clinical evidence confirming the diagnosis of knee OA, duration of pain was at least 6 months, radiological evidence of OA grades 2 and 3	Mean of all: 57.3 ± 9.4	RCT	(A) Polysaccharide-rich *Curcuma longa* extract (NR-INF-02) (500 mg twice daily) (B) Glucosamine sulfate (GS) (750 mg twice daily) (C) combination of NR-INF-02 and GS	Placebo (400 mg twice daily)	42 days	(1) Administration of NRINF-02 using VAS, WOMAC, and Global Impression Change (CGIC) at each clinical visit showed a significant decrease compared to placebo (2) NR-INF-02 treated group showed a significant decrease in the use of rescue medication, with clinical and subjective improvement compared to placebo (3) The tolerability and acceptability profile of NR-INF-02 was better during the trial period	4
Nakagawa et al. (2014), Japan [43]	50	Knee OA confirmed by radiographic	In: 71.9 ± 5.3/ Co: 66.1 ± 7.2	RCT	Theracurmin containing 180 mg/day of curcumin (developed a surface-controlled water-dispersible curcumin, named Theracurmin®)	Placebo)starch, dextrin, and maltose(	8 weeks	(1) Knee pain VAS scores were significantly lower in the Theracurmin group than in the placebo group, except in patients with initial VAS scores of 0.15 or less (2) Celecoxib dependence significantly deceased in Theracurmin than placebo (3) No major side effects were observed with Theracurmin treatment	4

(continued)

Table 16.1 (continued)

Author, year, country	Size	Inclusion criteria	Age Range (years) or mean	Study design	Intervention	Control	Duration	Main results	Jadad score
Panahi et al. (2014, 2016), Rahimnia et al. (2015), Iran [35–37]	40	Knee OA was based on the clinical and radiological criteria defined by the ACR and personal report of pain with mild-to-moderate degree on active movement	In: 57.32 ± 8.78/ Co: 57.57 ± 9.05	RCT	Curcuminoids (1500 mg/day in 3 divided doses)	Placebo	6 weeks	(1) Treatment with curcuminoids was associated with significantly greater reductions in WOMAC, VAS, and Lequesne's pain functional index (LPFI) scores compared with placebo (2) With respect to WOMAC subscales, there were significant improvements in pain and physical function scores but not stiffness score (3) A significant elevation in serum superoxide dismutase (SOD) activities and significant reduction in malondialdehyde (MDA) concentrations observed in curcuminoid compared with the placebo group (4) No significant changes in serum levels of interleukins 4 (IL-4) and 6 (IL-6), tumor necrosis factor-α (TNF-α), transforming growth factor-β (TGF-β), high-sensitivity C-reactive protein (hs-CRP), and erythrocyte sedimentation rate (ESR) found between groups (5) No considerable adverse effect in both groups	4[b]

Panda et al. (2018), India [46]	50	Suffering from unilateral or bilateral OA of the knee for greater than 3 months ACR criteria	In: 55.2 ± 8.6/ Co: 53.1 ± 8.3	RCT	Curene 500 mg once daily (Curene is a bioavailable formulation of turmeric *Curcucma longa* extract)	Placebo (microcrystalline cellulose)	3 months	(1) Significant reduction in WOMAC (total and in the pain, physical function scores and stiffness score) and VAS scores in the intervention compared with the placebo group (2) It had a good safety profile	5
Pinsornsak et al. (2012), Thailand [48]	88	Knee osteoarthritis according to the ACR (by history and physical examination)	45–80	RCT	Diclofenac at 75 mg/day + curcumin (curcuminoid capsules) at 1000 mg/day (study group)	75 mg/day Diclofenac with placebo control	3 months	No significant differences found regarding VAS for pain and KOOS scales	3
Shep et al. (2019), India [49]	139	ACR criteria for knee OA (confirmed by X-ray)	Curcumin: 53.1 ± 4.2/ Diclofenac: 52.1 ± 3.8	RCT	Curcumin (BCM-95®) 500-mg capsule 3 times daily	Diclofenac 50-mg tablet two times daily	28 days	(1) Similar improvement in the severity of VAS (pain) and KOOS (pain, symptoms, function in daily living, function in sport and recreation, and quality of life) scales found in two groups (2) Curcumin had weight-lowering effect and anti-ulcer effect (3) None of the patients required H2 blockers in the curcumin group and 19 patients required H2 blockers in the diclofenac group (0% versus 28%, respectively; $P < 0.01$) (4) Adverse effects were significantly less in the curcumin group (5) Patient and physician global assessment of therapy was similar in the two treatment groups	3

(continued)

Table 16.1 (continued)

Author, year, country	Size	Inclusion criteria	Age Range (years) or mean	Study design	Intervention	Control	Duration	Main results	Jadad score
Shin et al. (2017), South Korea [51]	25	Radiological diagnostic criteria for knee OA proposed by the ACR	T: 44.8 ± 5.4/T + E: 40.6 ± 7.7	Trial	(A) Theracurmin intake (T) group (capsule of 700 mg, 3 times per day, (total 2100 mg)) (B) Theracurmin is combined with exercise (T + E) (Theracurmin: with activity of curcumin increased 27-fold)	–	4 weeks	(1) The VAS was significantly decreased after 4 weeks in both group but the difference between groups did not significant (2) WOMAC score was significantly decreased in pain, physical function difficulties and total score but the difference between groups was not significant	1
Srivastava et al. (2016), India [47]	160	Suffering from knee OA was according to the guidelines by the ACR	In: 50.2 ± 8.1/ Co: 50.3 ± 8.6	RCT	*Curcuma longa* L. extract (500 mg) along with Diclofenac twice a day	Placebo capsules along with Diclofenac twice a day	4 months	(1) The VAS and WOMAC (total and pain, physical function and stiffness) scores improved in the intervention compared with the placebo group (2) IL-1b, ROS, and MDA significantly improved in the curcumin compared with the placebo group (3) *Curcuma longa* had no side effects compared with placebo	5

[a]No full text available (Epub ahead of print)
[b]Jadad score calculated for the study of Panahi et al. (2014) [36]

Outcome Score (KOOS) for assessing views of the patients about their knee- and osteoarthritis-related problems [38, 48, 49].

In comparison to controls, various curcumin formulations significantly improved the overall WOMAC scores in nine studies [35, 39, 40, 42, 44–47, 50], whereas one study did not see a significant difference between the intervention and control groups [41]. In one of these two studies, WOMAC scores were significantly decreased in both intervention groups (curcumin, curcumin plus exercise), although the differences between the groups were not significant [51].

Regarding VAS assessments, a significant decrease was observed in seven intervention groups compared to the placebo groups [35, 38, 43, 45–47, 49]. In one study, VAS scores were significantly decreased in both intervention groups (curcumin, curcumin plus exercise), although the differences between the groups were not significant [51]. However, two studies reported no significant differences for pain and knee injury in the treatment group [41, 48] compared to the placebo control group.

In cases where KOOS was assessed, scores were decreased in one study after intervention [39], although no significant differences were found in two studies between the intervention groups compared with placebo [48] or NSAID [49] treatments.

16.3.4 Other Outcomes and Quality Assessment

Some studies also assessed changes in various inflammatory markers in the interventional groups compared to the control. The most investigated inflammatory markers at follow up were C-reactive protein (CRP) [36, 39, 41]; interleukin (IL)-1β [36, 40, 41, 47]; IL-6 and erythrocyte sedimentation rate (ESR) [36, 40, 41]; and tumor necrosis factor-alpha (TNF-α) [36, 41]. After intervention, curcumin compounds led to significantly decreased levels of CRP [39], IL-6 and ESR [40], and IL-1β [40, 47], and two studies did not observe changes in biomarkers [36, 41]. Two studies showed that biomarkers of oxidative stress malondialdehyde (MDA), reactive oxygen species (ROS), and superoxide dismutase (SOD) were significantly reduced in the intervention groups compared with control groups [37, 47].

There were no severe adverse effects reported in nine studies [35–38, 41, 43, 46, 47, 49, 50]. Adverse effects were mostly manifested in the gastrointestinal system. However, Kuptniratsaiku et al. reported that curcumin showed better safety profiles than ibuprofen in terms of abdominal pain and distension [44]. Furthermore, of the 17 RCTs evaluated, only three studies were of low quality [39, 40, 51], as assessed by the Jadad scoring system and one study had no full text [42].

16.4 Discussion

16.4.1 Summary of Evidence

The main objective of this systematic study was to identify improvements in the WOMAC and VAS scores from baseline to post-intervention in clinical trials of curcumin-related treatments. We found that oral administration of various curcumin formulations could improve VAS and overall WOMAC scores significantly with no severe adverse effects after a minimum of four weeks of treatment. However, some curcumin preparations were more effective in improving knee stiffness.

The WOMAC index is a global questionnaire that measures the health status of osteoarthritis patients using 24 items divided into three subscales. It is generally used in the evaluation of patients with osteoarthritis knee and hip to evaluate the effects of various interventions [52]. The subscales of the WOMAC assessment consist of various aspects of osteoarthritis, including pain, stiffness, and physical function [53]. Belcaro et al. showed that 200 mg of curcumin-phosphatidylcholine compound (known as Meriva®) per day improved overall WOMAC scores and also the various components including pain sensation, joint stiffness, and physical function after 3 months treatment of osteoarthritis patients [39]. The mobility assessed by walking performance (treadmill) also increased after treatment with curcumin-phosphatidyl-choline compared with a standard treatment. These results were confirmed by a subsequent study by the same research team which

investigated the long-term efficacy and safety of the curcumin-phosphatidyl-choline compound over a longer time period (8 months) in 100 patients with osteoarthritis [40]. They showed that the global WOMAC score significantly decreased by 58% after treatment with the curcumin–phosphatidyl–choline compound. There was also a reduction in inflammation indicated by changes in CD40L, IL-1β, IL-6, and ESR biomarkers. Another study showed a significant improvement in global WOMAC scores after treatment with a 350 mg curcuminoid and 150 mg boswellic acid complex for 3 months compared to standard care [51]. However, the positive effects were observed only in the subscale of physical performance tests. In addition, studies conducted by Panahi et al. found a significant improvement in total WOMAC scores following treatment with a curcuminoid complex (1500 mg/day in 3 divided doses) for 6 weeks [35–37]. However, with respect to WOMAC components, the improvement was detected only in the pain and physical function scores but not in stiffness scores.

In studies of curcumin extracted from turmeric, Shin et al. investigated the effect of the physiologic activity of 90 mg/day curcumin in 25 patients with knee osteoarthritis for 4 weeks and showed that total WOMAC score was significantly improved by the intervention, although there was no control group in this study [51]. However, a dosage of 180 mg/day of curcumin in a study of 50 subjects for 8 weeks was found to reduce knee pain [43]. Additionally, the use of a *Curcuma longa* extract at a different dosage significantly reduced overall WOMAC scores [44–47] as well as WOMAC subscales [46]. It is known that curcumin compounds have antioxidant properties and can facilitate scavenging of free radicals such as reactive oxygen and nitrogen species [54, 55]. These natural dietary antioxidants can also modulate the activity of glutathione (GSH), catalase, and SOD enzymes and thereby inhibit the production of inflammation by chondrocytes in OA patients, especially with a treatment duration of more than 6 weeks [56, 57]. In spite of its reported benefits via inflammatory and antioxidant mechanisms, curcumin has poor bioavailability due to its poor absorption, rapid metabolism, and excretion [58, 59]. To overcome this problem, there are now several types of curcumin preparations with varying oral bioavailability and stability [60–62]. A number of studies have shown that curcumin nanoparticles have a significantly higher bioavailability compared to free curcumin crystals [63]. This supports the idea that nanocurcumin supplementation could manage knee osteoarthritis complications such as the pain and stiffness of joints better than other curcumin compounds [42, 64]. The results of another study also suggested that a curcumin formulation with a lipid component (Meriva) has more bioavailability than unformulated curcumin [65]. Therefore, variations in bioavailability may explain the observed differing effects of the various curcumin preparations on components of WOMAC, such as knee stiffness.

Despite the overall improvement as seen with WOMAC scores, there were no significant differences between the patients taking anti-inflammatory drugs (400 mg ibuprofen) alone and those who were treated with 400 mg solid lipid curcumin and anti-inflammatory medications for 3 months [41]. However, Srivastava et al. showed that diclofenac with supplementary curcumin treatment led to a significant improvement in ROS and MDA levels as well as VAS and WOMAC scores, and this was better than diclofenac treatment alone [47]. This shows that curcumin could be as effective as an anti-inflammatory medication on WOMAC global function scores in osteoarthritis. However, additional studies are needed to confirm these findings.

This systematic review represents the highest level of available evidence which shows that different curcumin compounds are generally able to reduce overall WOMAC scores and some WOMAC subscales such as pain and physical function. In addition, some products such as curcumin phosphatidylcholine (lipid-based curcumin) [39] and nanocurcumin [42] can also modulate the stiffness subscale compared to placebo, most likely due to their increased bioavailability [66, 67].

In addition, the results of the present study demonstrate the efficacy of different types of curcumin mixtures in alleviating VAS scores in the intervention groups compared to placebo. This instrument has been designed to measure pain

intensity and has also been used in various populations, including those with chronic diseases such as osteoarthritis [68, 69]. In the study by Henrotin et al., both low (2 × 2 46.67 mg capsules/day) and high (2 × 3 capsules/day) dosages of bio-optimized *Curcuma longa* extracts for 3 months decreased the Patient Global Assessment of Disease Activity (PGADA) and VAS scores, compared to placebo, in 150 patients with osteoarthritis [38]. The adverse events related to the product were similar in the placebo and the treatment groups. Similarly, intake of 100 or 500 mg / day of the bio-optimized extract had similar results over treatment periods of 3 and 12 weeks, respectively [45, 46]. Moreover, Nakagawa et al. indicated improvement in the VAS score after 8 weeks of treatment with 180 mg/day of curcumin (Theracurmin) compared to its control [43]. Interestingly, dependence on Celecoxib was significantly reduced in the intervention group compared to the placebo. In addition, Shin et al. demonstrated that treatment with 90 mg/day curcumin (Theracurmin) for 4 weeks could also improve VAS scores without side effects [51]. Furthermore, in the other three studies [35–37], the administration of curcuminoids (1500 mg/day in 3 divided doses) was associated with significantly greater reductions in VAS scores and MDA concentrations. However, no significant changes were observed in the serum levels of IL-4, IL-6, TNF-α, transforming growth factor-β (TGF-β), CRP, and ESR between groups. Although osteoarthritis is a complex condition that affects different joints, many previous studies have indicated that progression is significantly related to oxidative stress and ROS. ROS-induced damage leads to an increase in the irritation of the nerves resulting in pain in the synovial, bone, and soft tissues [70]. The mechanism underlying the analgesic effect of curcumin may be based on the elevation of serum SOD and GSH levels and the reduction of MDA serum levels through its antioxidant activity [56, 71]. In turn, this would lead to an improved oxidant status, increased joint mobility, and reduced pain in patients with osteoarthritis [35–37, 47].

Nevertheless, it should be noted some types of curcumin preparations (solid lipid curcumin or curcumin) did not result in a significant difference in the VAS scores compared to the control group receiving anti-inflammatory agents, diclofenac or ibuprofen) [44, 49]. However, both groups showed clinical improvements after medication. It should also be noted that the effectiveness of curcumin as a supplement in combination with the anti-osteoarthritic medications in the treatment of primary knee osteoarthritis was more effective than anti-osteoarthritic drugs alone [47].

The results of the study which used curcumin to evaluate the changes in short- and long-term symptoms and function of patients with a knee injury, using KOOS assessment, showed significant positive changes over time compared to placebo [38]. However, these changes were not significant when the control group received anti-inflammatory drugs [49]. Based on these results, it can be concluded that curcumin compounds can be effective in reducing symptoms and improving function in osteoarthritis patients. These compounds are also safe and well tolerated.

16.4.2 Limitations

Although our study indicated the promising role of various curcumin compounds in the improvement of function and reduction of pain using three global questionnaires (WOMAC, VAS, and KOOS) in patients with knee osteoarthritis for several durations, there were some limitations. The scales used as the main outcome in the mentioned studies are based on the patient perspectives of their symptoms. Secondly, the measurement of circulating metabolites after consumption of different curcumin compounds in the above studies should be taken into account in the interpretation of the results. Another common limitation shown in these studies is the lack of sufficient data to compare the bioavailability of the different curcumin compounds used together and there are also no comprehensive studies comparing the efficacy of different curcumin combinations in the management of osteoarthritis. Higher quality RCTs should be designed specifically to examine the role of different types of curcumin preparations as a supplementary therapy from the perspective of their metabolites and the bioavailability of various curcumin compounds.

16.5 Conclusion

This review provides evidence that different types of curcumin complexes are beneficial as an alternative or complementary medication for osteoarthritis treatment. Curcumin and various curcumin compounds reduced VAS and WOMAC scores in all the reviewed studies. Curcumin compounds with more bioavailability have a more positive effect on knee stiffness.

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