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Review

Efficacy and safety of *Curcuma longa* extract as a treatment of primary knee osteoarthritis in adults and elderly: a systematic review

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Abstract. Osteoarthritis (OA) is a chronic disease that leads to the wearing of joints cartilage, the most common being knee OA. The aim was to identify the efficacy and safety of *Curcuma longa* extract as a potential treatment for knee OA in adults and elderly. A systematic review was conducted on different databases, using a search strategy that included curcumin, curcuma, turmeric, dietary/food/herbal supplement, phytochemical, plant extract, nutraceutical and osteoarthritis as keywords. Inclusion criteria were double-parallel randomized clinical trials in adults, diagnosed with knee OA, and published within the last 10 years. Only studies that used turmeric, not any other herbaceous substance, were included. Five studies were included. VAS, WOMAC, JKOM and KOOS scales were used. Inflammation and oxidative stress and cartilage degradation biomarkers were controlled. Statistically significant reductions in VAS, WOMAC (except stiffness) and biomarkers were observed. Curcumin may have therapeutic utility in knee OA, showing similar efficacy to conventional drug treatment, but presenting fewer adverse effects.

Key words: curcumin, Curcuma longa, osteoarthritis, knee, treatment

Introduction

Osteoarthritis (OA) occurs when the cartilage between the joints breaks down, which can cause stiffness, pain and a decrease in mobility (1). It is one of the most prevalent diseases within the elderly population (80% of the population aged 65 and older) (2,3) predominant in females (1). The most frequently affected joints are knees, hands, feet, hip and spine, although it can also affect shoulders and ankles (4,5).

The American College of Rheumatology (ACR) classification criteria (6) for knee OA are 1) knee pain for most days of the previous month; 2) crepitus on the active mobilization of the joint; 3) morning stiffness <30 minutes; 4) age >38 years and 5) bony enlargement. The patient must meet criterion 1 together with one of the following combinations: [2,3,4], [2,5] or [4,5], sensitivity must be ≥89% and specificity ≥88%.

The Visual Analogue Scale (VAS) (4) is used to assess the intensity of pain, with a range from 0-10 or from 0-100, 10 or 100 being the highest intensity and 0 the absence of pain. There are other specific methods of OA assessment, among which the most representative is the *Western Ontario and McMaster Universities Osteoarthritis Index* (WOMAC) questionnaire (7). The Japanese Knee Osteoarthritis Measure (JKOM) (8) is a self-administered tool specific for knee OA that, as well as WOMAC scale, has international validity; and the Knee injury and Osteoarthritis Outcome Score (KOOS) (9) is a self-administered tool for the classification of knee OA symptoms.

There is currently no cure for OA. Its treatment is palliative (1) and can be divided into prevention or primary intervention (weight control, injury prevention and orthopedic treatment), secondary intervention (early diagnosis) and tertiary intervention (improve pain and joint mobility through weight loss, physical activity, disease education, rehabilitation services and pharmacological treatment and/or surgery) (10,11).

Turmeric is a tropical plant in the ginger family native to South/Southeast Asia (12). Turmeric has been used for thousands of years for its health benefits (antioxidant, anti-inflammatory, antimicrobial, antimutagenic, anticancer), although the mechanisms of action of its curcuminoids had not been researched until recently (13–15). Curcuminoids, including the curcumin, the main bioactive compound in turmeric, have already shown anti-inflammatory and antioxidant properties and pain-relief action in numerous in vitro and animal studies (14,16). However, the available scientific evidence about its efficacy in humans is still limited. In literature, similar uses of plants have been identified in neighboring regions in the treatment of rheumatism, such as *Muscari neglectum* Guss., *Eryngium* species, *Rosa* species and *Urtica dioica* L due to their antioxidant and anti-inflammatory activities (17).

The main objective of this review is to analyse whether turmeric, in particular curcumin or turmeric extract, may have benefits in the treatment of knee OA in adults, due to its anti-inflammatory and pain-relieving properties. The secondary aims are (i) to analyse the efficacy and adverse effects of curcumin or *Curcuma longa* L. (*C. longa)* extract, (ii) to determine the dose for an optimal balance between benefits and adverse effects, (iii) to compare the efficacy and safety of curcumin to placebo or conventional treatment with paracetamol or NSAIDs and (iv) to study the possible anti-inflammatory effects of curcumin.

Experimental section

Data sources and search strategies

This review was designed as a literature-based descriptive study. A research question (PICO) was elaborated to elucidate whether curcumin and *C. longa* L. extract are effective and safe for the treatment of knee OA in adults and elderly. Databases used were PubMed, Scopus, Scielo, Cochrane and Web of Science. Bibliographic search spanned from January to February 2020. The search strategies were carried out using the DeCS and MeSH descriptors, together with the Boolean operators AND and OR (Table 1). This systematic review was submitted to PROSPERO for its registration.

Eligibility criteria

Studies on adult and elderly population (18 years and older) suffering from knee OA (patients, P); studies using curcumin or *C. longa* L. extract as a food

Table 1. Keywords used in the literature search

Data base	DeCS-MeSH combinations
PubMed	(curcumin* OR curcuma OR turmeric OR turmeric OR "dietary supplement*" OR "food supplement*" OR "herbal supplement*" OR phytochemical* OR "Plant extract*" OR nutraceutical*) AND osteoarthritis AND "randomized controlled trial"[Publication type]
Cochrane	(curcumin* OR curcuma OR turmeric OR turmeric OR "dietary supplement*" OR "food supplement*" OR "herbal supplement*" OR phytochemical* OR "Plant extract*" OR nutraceutical*) AND osteoarthritis AND "randomized controlled trial"[Publication type]
Scielo	((curcumin* OR curcuma OR turmeric OR turmeric OR "dietary supplement*" OR "food supplement*" OR "herbal supplement*" OR phytochemical* OR "Plant extract*" OR nutraceutical*) AND osteoarthritis)
Scopus	(TITLE-ABS-KEY ((curcumin* OR curcuma OR turmeric OR turmeric) AND osteoarthritis) AND DOCTYPE (ar) AND (LIMIT-TO (EXACTKEYWORD, "Human"))
Web of Science	(curcumin* OR curcuma OR turmeric OR turmeric OR "dietary supplement*" OR "food supplement*" OR "herbal supplement*" OR phytochemical* OR "Plant extract*" OR nutraceutical*) AND osteoarthritis AND "randomized controlled trial"[Publication type]

supplement (intervention, I); studies comparing the use of curcumin or *C. longa* L.extract with placebo or pharmacological treatment (comparison, C); and studies describing changes in VAS, WOMAC, JKOM and KOOS indexes and sColl2-1, ROS and IL-1B markers (outcome, O) were eligible. Only original randomized controlled trials in humans, studies in English and Spanish, and studies published from 2010 onwards were considered. A JADAD score of above 3 and adherence with CONSORT 2010 criteria were required to ensure good quality and to reduce any potential bias.

Studies on patients under age; those that involved a combination of curcumin or *C. longa* L. extract with other substances (e.g. piperine, volatile oil, boswellic acid); those that did not compare it to placebo or pharmacological treatment; and those using different scales or markers to the ones mentioned in the inclusion criteria were excluded. Studies where only one of the study groups fulfilled the inclusion criteria were also excluded. Literature research was carried out by two researchers separately, and then the results were compared. Duplicate studies were excluded. An evaluation of the selected studies was carried out based on the CONSORT statement and the JADAD scale.

Data collection

The data compilation from each study was performed in SPSS 24.0 statistical software package (IBM Corp. Armonk, NY: USA). The following variables were recorded: first author's name and year of publication, country of study, study design, sample size (men/women), average age, diagnostic criteria for knee OA, exclusion criteria, duration of intervention, food supplement and dose, treatment in control group and dose, outcomes and adverse effects.

Results

Search results and study characteristics

Figure 1 shows the flowchart of the article selection process. 388 articles were selected for screening.

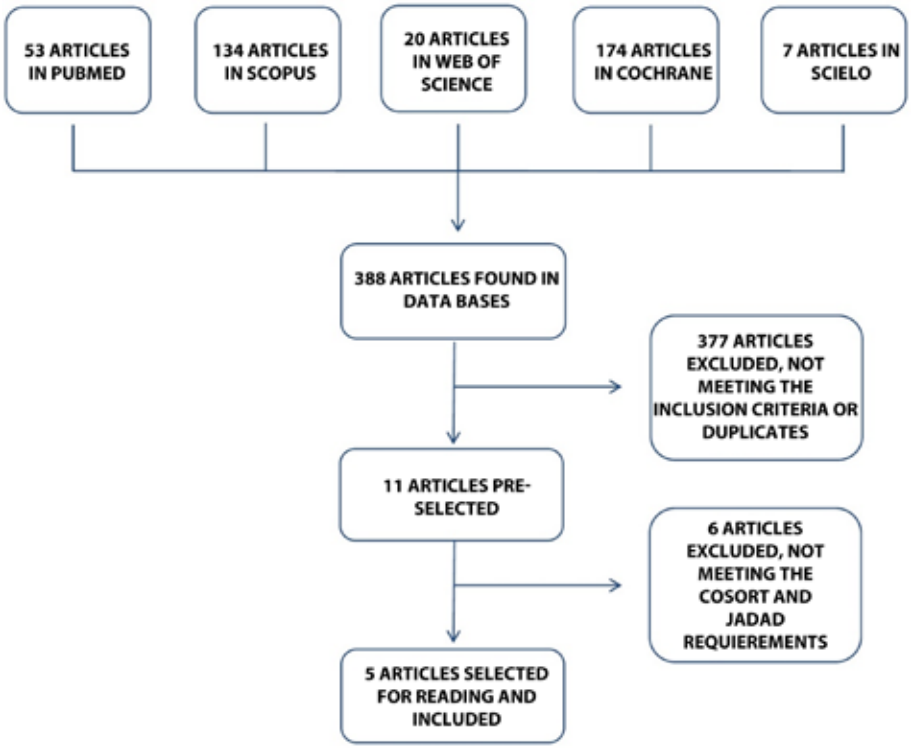

Figure 1. Article selection flowchart

377 articles that did not meet the inclusion criteria or were duplicates were excluded. The search narrowed down to 11 studies, assessed for full-text eligibility, but only 5 studies were finally included after applying the CONSORT statement and the JADAD scale. A risk of bias assessment was performed, assessing the selection (random sequence generation, allocation concealment), performance (blinding of participants and personnel), detection (blinding of outcome), attrition (incomplete outcome data) and reporting (selective reporting) processes, where applicable. No major bias were identified.

Study characteristics

The general characteristics of the studies selected in this review are summarized in Table 2. Four studies were carried out in Asia (Thailand (18), India (19,20), Japan (21)) and one in Europe (Belgium (22)). The sample size ranged from 41-367 participants. Most participants were women (Table 2). Participants age ranged from 40-80 years, with a mean age of 60 years in Kuptniratsaikul et al. (18), 68.7 years in Nakagawa et al. (21) and 61.9 years in Henrotin et al. (22). Both studies carried out in India (19,20) had a significantly lower mean age, from 50-55 years. Most of the studies (n=4) presented an experimental group (EG) and a control group (CG). Henrotin et al. (22) was the only one that presented 3 groups, 2 EG and 1 CG (Table 2).

Curcumin or *C. longa* L. extract was used in the EG in all studies (n=5). Placebo was used in the CG in most studies (20–22), but Kuptniratsaikul et al. (18) used ibuprofen, and Srisvastava et al. (19) used diclofenac (Table 2). However, the doses used in the EG differed remarkably between studies, ranging from 180 mg/day to 1500 mg/day. Two different doses were used by Henrotin et al. (22): 186.6 mg/day (low dose group) and 279.9 mg/day (high dose group). Curcumin was dispensed 1-3 times/day in 1-3 capsules. In all 5 studies, the CG received the same number of placebo or drug capsules a day (Table 2).

The duration of the intervention varied from 4 to 16 weeks. All studies (n=5) used the ACR criteria for the diagnosis of knee OA (Table 2). Three studies (18–20) used the WOMAC scale and its subscales. Henrotin et al. (22) used the KOOS scale and its subscales; and Nakagawa et al. (21) used the JKOM scale. Only two studies (19,20) which used WOMAC scale reported both initial and final scores, before and after the intervention. In all studies (18–22) a considerable decrease of the indexes after the intervention was observed. The VAS scale was used in all studies, except for Kuptniratsaikul et al. (18), and all showed a reduction in the final VAS score (Table 3). Lastly, all studies had a JADAD score of 4 (19) or 5 (18,20–22), making them eligible according to the inclusion criteria (JADAD score >3). All included studies (n=5) were randomized double-blind clinical trials.

[a]WOMAC, Western Ontario and McMaster Universities Arthritis Index; [b]VAS, Visual Analogue Scale; [c]JKOM, Japanese Knee Osteoarthritis Measure; [d]KOOS, Knee Injury and Osteoarthritis Outcome Score; [e]EG, experimental group; ND, no data.

Results synthesis and adverse effects

A total of 367 people (30 men, 337 women) with a mean age of 60 years were enrolled for 4 weeks in Kuptniratsaikul et al. (18). They were divided into an experimental group (n=185), in which participants took 1500 mg of Turmeric extract/day in 2 capsules 3 times/day, and a control group (n=182), who took 1200 mg ibuprofen/day (2 capsules 3 times/day). Controls and measurements of the WOMAC scale were carried out every 2 weeks. The efficacy of turmeric was non-inferior to that of ibuprofen, since the WOMAC total score and its pain and functionality subscales score reached statistical significance. However, the number of adverse effects cases (bloating, abdominal pain, nausea and dyspepsia) was higher in the ibuprofen group (p=0.222). Participant's satisfaction after the intervention was similar in both groups (96-97%).

Forty-one people (9 men, 32 women) with a mean age of 68.7 years participated for 8 weeks in the study by Nakagawa et al. (21). They were divided into an experimental group (n=18), taking a daily dose of 180 mg curcumin in 2 capsules 3 times/day, and a control group (n=23), taking the same dose of placebo. Participants' symptoms were evaluated at weeks 0, 2, 4, 6 and 8, according to the VAS and the JKOM scales. They were asked to record NSAIDs intake. At 8 weeks, a reduction in the VAS scale values was

Table 2. Characteristics of the studies included in the review

Author, year	Country	Design	n (M[a]/F[b])	Mean age [range] (years)	OA[c] diagnostic and inclusion criteria	Exclusion criteria	Duration (weeks)	Experimental group	Control group	Variables studied
Kuptniratsaikul MD, 2014 (18)	Thailand	DB[d]	367 (37/337)	60.0 [>50]	Primary knee OA, ACR[e] criteria	Impaired kidney or liver function, peptic ulcer, allergy to curcumin or ibuprofen	4	Curcuma extract. 1500 mg/day (2 capsules 3 times a day)	Ibuprofen 1200 mg/day (2 capsules 3 times/day)	WOMAC[f] (total, pain, stiffness and functionality)
Srivastava S, 2016 (19)	India	DB	160 (57/103)	EG[g]: 50.24 CG[h]: 50.27 [40-80]	Primary knee OA, ACR criteria	Patients with RA[i], DM[j], RI[k] liver or CV[l] conditions, or pregnant women	16	*Curcuma longa* extract 500 mg/day (1 capsule/day)	Placebo 1 capsule/day	WOMAC, VAS[m]
Panda S, 2018 (20)	India	DB	468	EG: 55.20 CG: 53.12 [40-75]	Primary knee OA, ACR criteria, BMI[n] 18-30 kg/m^2	Pregnant or lactating, allergy to NSAIDs[o], RA, surgery 3 months before the study, injuries 4 months before the study, CV, renal, endocrine, pulmonary, hepatic, gastrointestinal, neurological or psychiatric conditions, abuse of drugs, corticosteroids, glucosamine and chondroitin 3 months before the study, or intra-articular treatments	8	*Curcuma longa* extract 500 mg/day (1 capsule/day)	Placebo 1 capsule/day	WOMAC, VAS
Author, year	Country	Design	n (M[a]/F[b])	Mean age [range] (years)	OA[c] diagnostic and inclusion criteria	Exclusion criteria	Duration (weeks)	Experimental group	Control group	Variables studied

Table 2 (*Continued*)

Table 2. Characteristics of the studies included in the review

Author, year	Country	Design	n (M[a]/F[b])	Mean age [range] (years)	OA[c] diagnostic and inclusion criteria	Exclusion criteria	Duration (weeks)	Experimental group	Control group	Variables studied
Nakagawa Y, 2014 (21)	Japan	DB	41(9/32)	68.7 [>40]	Primary knee OA, ACR criteria	Previous knee surgery, intra-articular treatments, steroid injections 2 months before the study	8	180 mg curcumin (3 capsules 2 time a day)	Placebo 3 capsules 2 times/day	VAS scale, JKOMp scale (stiffness and pain, quality of life, general activities, general conditions)
Henrotin Y, 2019 (22)	Belgium	DB	150 (47/103)	HDG[q]: 60.9 LDG[r]: 61.4 CG: 63.3 [45-80]	Primary knee OA, ACR criteria	Patients with dementia, pregnancy or lactation, recent surgery, curcumin allergy, recent knee trauma, use of intra-articular injections 3 months before the study, oral corticosteroid therapy for 3 months, heparin	12	*Curcuma longa* extract LDG: 186.6 mg/day (2 capsules 2 times/day) + 2 placebo capsules (once a day) HDG: 279.9 mg/day (2 capsules 3 times/day)	Placebo 3 capsules/day	KOOS[s], VAS (PGADA[t])

[a]M, masculine; [b]F, feminine; HDG, high-dose group; [c]OA, osteoarthrosis; [d]DB, double blind; [e]ACR, American College of Rheumatology; [f]WOMAC, Western Ontario and McMaster Universities Arthritis Index; [g]EG, experimental group; [h]CG, control group; [i]RA, rheumatoid arthritis; [j]DM, diabetes mellitus; [k]RI, renal insufficiency; [l]CV, cardiovascular; [m]VAS, Visual Analogue Scale; [n]BMI, body mass index; [o]NSAID, Nonsteroidal anti-inflammatory drugs; [p]JKOM, Japanese Knee Osteoarthritis Measure; [q]HDG, high-dose group; [r]LDG, low-dose group; [s]KOOS, Knee Injury and Osteoarthritis Outcome Score; [t]PGADA, Patient Global Assessment of Disease Activity.

Table 3. Outcomes of the studies included in the review.

Author, year		WOMAC[a] total (initial/ final; difference)	WOMAC[a] pain (initial/ final)	WOMAC[a] stiffness (initial/ final)	WOMAC[a] functionality (initial/final)	VAS[b] (initial/ final)	JKOM[c] (initial/ final)	KOOS[d] final	
Kuptniratsaikul MD, 2014 (18)	Ibuprofen	3.23 ± 1.97	3.17 ± 1.98	3.16 ± 2.36	3.26 ± 2.05	ND	ND	ND	
	Curcuma	3.36 ± 2.04	3.25 ± 2.11	3.28 ± 2.38	3.41 ± 2.09	ND	ND	ND	
	P-value	p=0.01	p=0.018	p=0.06	p=0.01	ND	ND	ND	
Srivastava S, 2016 (19)	Curcuma	ND	15.10/9.48	5.55/4.08	54.03/32.12	7.94/4.03	ND	ND	
	Placebo	ND	15.29/10.16	5.31/4.16	50.99/33.88	7.66/5.11	ND	ND	
	P-value	ND	p=0.001	p=0.73	p=0.008	p=0.0001	ND	ND	
Panda S, 2018 (20)	Curcuma	ND	8.24/4.28	4.52/2.12	25.12/12.04	52.37/27.76	ND	ND	
	Placebo	ND	8.16/6.96	4.72/3.76	24.48/20.04	52.79/44.83	ND	ND	
	P-value	ND	p<0.05	p<0.05	p<0.05	p<0.05	ND	ND	
Nakagawa Y, 2014 (21)	Curcuma	ND	ND	ND	ND	0.52/0.20	0/-17	ND	
	Placebo	ND	ND	ND	ND	0.42/0.21	0/-12	ND	
	P-value	ND	ND	ND	ND	p=0.023	p>0.05	ND	
Henrotin Y, 2019 (22)	HDG	ND	ND	ND	ND	-29.5mm p<0.001	ND	Total Pain Symptoms Daily functionality Sports functionality Quality of life	56.3 12.3 10 11.1 11.1 12.4
	LDG	ND	ND	ND	ND	-36.5 mm p<0.001	ND	Total Pain Symptoms Daily functionality Sports functionality Quality of life	48 12.8 7.4 9.6 9.6 9.2
	Placebo	ND	ND	ND	ND	-8 mm p=0.051	ND	Total Pain Symptoms Daily functionality Sports functionality Quality of life	42.1 10.8 7.5 9.7 9.7 6.6
	P-value	ND	ND	ND	ND	p=0.018 (between EG[e] and Placebo)	ND	p>0.05	

observed, being statistically significant when the initial value was ≥0.15. A greater improvement was observed in the experimental group in each of the JKOM subscales, especially at weeks 6 and 8, with no statistical significance. The number of rescue NSAID intakes was significantly lower in the experimental group (p=0.025). No adverse effects were observed except for two cases of hypertension and itchy tongue in the experimental group.

One hundred and sixty people (57 men, 103 women) with a mean age of 50 years participated for 16 weeks in the study by Srivastava et al. 2016 (19). Participants were divided into an experimental group (n=78), which took 500 mg of *C. longa* L.extract in 1 capsule once a day, and a control group (n=82), which took the same dose of placebo in capsules and 500 mg of diclofenac. Radiological and analytical controls were performed at weeks 0, 8 and 16. The VAS and WOMAC pain and functionality scales significantly improved, with no statistically significant improvement on the stiffness subscale. In addition, they measured biomarkers of inflammation (IL-1B cytokines) and oxidative stress (reactive oxygen species), which were also significantly reduced. Radiographies did not show any improvement. Two (dyspepsia n=1 and nausea n=1) and four (dyspepsia n=2, nausea n=1 and constipation n=1) specific cases of adverse effects were observed in the experimental group and the placebo group, respectively.

The study by Panda et al. 2018 (20) involved 46 people with a mean age of 54 years, divided into two groups. The experimental group (n=24) took a 500 mg capsule of *C. longa* L. extract a day, and the control group (n=22) took a placebo capsule a day. The intervention lasted 8 weeks and follow-ups were made on days 0, 2, 7, 14, 30 and 60. Blood and urine tests and physical examination were performed and participants' symptoms were evaluated according to the VAS and WOMAC scales. The placebo group showed statistically significant improvements in pain, stiffness and functionality subscales from day 7 and kept improving progressively throughout the rest of the intervention. There was also a statistically significant improvement on the VAS scale. Adverse effects occurred in 12% of the experimental group (headache n=1, abdominal distension n=1 and abdominal pain n=1); and in 8% of the control group (reflux n=1 and headache n=1). The use of rescue NSAIDs was lower in the experimental group (n=3) compared to the placebo group (n=7).

In the study by Henrotin et al. (22), 150 people (47 men, 103 women) with a mean age of 61.9 years participated for 12 weeks. Participants were divided into 3 groups. The high dose experimental group (n=49) took 279.9 mg of *C. longa* L. extract in 2 capsules 3 times/day. The low dose experimental group (n=47) took 186.6 mg of the extract divided into 2 capsules 2 times/day plus 2 placebo capsules. The control group (n=45) took placebo in 2 capsules 3 times/day. The outcomes were measured using the VAS and the KOOS scale and its subscales. The intake of acetaminophen and rescue NSAIDs was also recorded. Serum levels of Coll2-1, a biomarker of cartilage degradation, were monitored (22). Regarding the VAS scale, a reduction in all 3 groups was observed, being statistically significant in the two experimental groups and not significant in the placebo group. A not statistically significant reduction of sColl2-1 in both experimental groups and a slight increase in the control group were also observed. Regarding the KOOS scale, an improvement in all groups was observed and, although it was greater in the experimental groups, the difference between groups was not statistically significant. Adverse effects (diarrhea and digestive discomfort) occurred mainly in the high-dose experimental group (37%), compared to the low-dose (21%) and the placebo (13%) groups. The low-dose experimental group showed a statistically significant decrease in rescue NSAID intake. All 3 groups reported a similar decrease on Paracetamol intake, showing no statistically significant differences.

Discussion

Turmeric has been widely used in oriental cuisine and medicine (12,15,23). The numerous health benefits of its bioactive compounds, curcuminoids (including curcumin), have recently been the target of scientific research (13,15). The studies conducted to date in animals and humans have indicated that turmeric does have anti-inflammatory and pain relief properties (12,13,15,23). Furthermore, it is recognized as a

safe substance even at high doses (14,16). However, some studies suggest that its therapeutic actions could be diminished in a significant percentage as curcuminoids may exhibit very poor solubility in water and therefore the systemic bioavailability could be very low (24). Despite the latter, its properties, together with its safety of use, have motivated studies on its possible use in treating OA (16,25). OA is a chronic and limiting disease. The existing treatment focuses on improving the symptoms (pain, joint stiffness and decrease in mobility, among others) (26,27). Knee OA is the most common and the most scientifically studied regarding this pathology (21).

The objective of this review was to identify and evaluate the studies conducted in the last 10 years on curcumin or Turmeric extract in relation to OA, its possible benefits and associated adverse effects, compared to conventional pharmacological treatment or placebo.

The most up-to-date scientific evidence on this topic shows that turmeric has anti-inflammatory effects on the synovial joint of the knee and seems to be as effective as the current conventional treatment with paracetamol or NSAIDs. It helps fight the pain and improves joint functionality. It also seems to cause fewer gastrointestinal adverse effects than the pharmacological treatment. However, more studies are needed to corroborate the latter as well as to identify the ideal dose to achieve the optimal efficacy/safety balance.

When we first searched for scientific evidence on turmeric's health benefits, a great variety of studies on this topic was found. However, after evaluating their methodologic quality according to our inclusion criteria, the number of valid studies was narrowed down to 5. A statistically significant improvement was observed in all 4 studies (19–22) in which the VAS scale for pain was used. The final score of the VAS scale was statistically significant when compared to the initial scores and the control group scores. Based on these results, curcumin could be an effective treatment for relieving knee OA pain within a relatively short period of time (4 to 16 weeks). In some studies (20,21) the significant improvement is even reflected from week 2. It must be taken into account that the VAS scale is biased, as the patient evaluates their own perception of pain. Due to the low number of studies, their short duration and the small sample sizes, no firm conclusions could be drawn.

Regarding the WOMAC pain subscale, similar reduction in pain scores were observed in both curcumin and ibuprofen groups (18), and the reduction was even greater in curcumin groups when compared to placebo (19,20). As for the WOMAC stiffness subscale, only one (20) of the 3 (18–20) studies that used this scale reached statistical significance. This could be due to the use of ibuprofen (18) and diclofenac (19) in the control group instead of placebo (20). Results were unanimous regarding the WOMAC subscale of functionality. Statistical significance was reached in all 3 studies.

In Henrotin et al. (22), the knee joint functionality was assessed using the KOOS scale. This scale was divided into two subscales, Function in daily living and Function in sport and recreation. However, neither of these two subscales reached statistical significance. A greater improvement in daily life functionality was observed in the low-dose group, and a greater improvement was observed in sport practice functionality in the higher-dose group. However, the study does not mention which activities did the participants perform, nor the training intensity, or frequency. Given the mean age of participants, they might have only performed moderate physical activity, if any. Thus, the information obtained from function in sport and recreation subscale might not lead to further conclusions. The improvement on other symptoms and knee-related quality of life subscales was more representative in the *C. longa* extract low-dose group. However, it did not reach statistical significance. In addition, this group presented fewer adverse effects. Therefore, it seems that curcumin dose is not directly proportional to its efficacy nor to adverse effects. However, conclusions cannot be drawn solely from this study.

Overall, firm conclusions cannot be drawn due to the following: WOMAC, KOOS and VAS scales are based on a biased assessment since participants evaluate their own symptoms; all interventions lasted from 4-16 weeks, meaning that long-term effects of curcumin have not been studied; every study used different dosages, and there were differences on the demographic characteristics of study participants.

Nakagawa et al. (21) shared only the JKOM total score and did not specify the results of its subscales. It only reported a greater improvement in the experimental group, without statistical significance. Therefore, it is not possible to draw any firm conclusion, although the improvement observed is similar to the results shown in previously mentioned studies. Furthermore, even though it is internationally validated, the JKOM scale is intended for the Japanese population, which makes it difficult to compare to other scales.

sColl2-1, an indicator of knee cartilage degradation, was measured in only one study (22), where a greater but not statistically significant improvement was reported in the experimental groups compared to the control group. Significant differences were observed in the biomarkers of inflammation (IL-1B) and oxidative stress (ROS) in Srivastava et al. study (19). However, firm conclusions could not be drawn due to the lack of evidence, since this was the only study that included those variables. Knee OA was initially thought to be merely mechanical, however, it is currently known that it causes inflammation and oxidative stress in the chondrocytes of the joint (2,28). Despite the fact that there are no studies in humans, there are in vitro studies (29,30) and studies in bovine chondrocytes (14,25) which report that curcumin acts as an antiapoptotic on chondrocytes and inhibits inflammatory mediators such as interleukins, including IL-1B (19), and prostaglandins PEG2 and ROS (nitric oxide) (14,16,25,31).

This systematic review was not able to reach a conclusion on the dose of *C. longa* L. needed to exert beneficial effects. Among other reasons, this is due to the heterogeneity of the samples, the different intervention durations, different control group strategies (placebo/pharmacological treatment) and the small number of studies that are currently available (n=5). Overall, the significance between the different doses was similar in all studies and there seems to be no direct proportion between dose and efficacy. A larger number of adverse effects may appear when intaking high doses of curcumin, although it produces fewer and milder effects than NSAIDs.

Although curcumin appears to have promising effects on knee OA, more randomized clinical trials are needed. Future studies should alleviate limitations, such as the sample size and the duration of the intervention, since studies to date do not allow to observe the efficacy of *C. longa* L. and the development of long-term adverse effects. Likewise, the optimal curcumin dose for treatment of knee OA still needs to be determined. Future research should also be aimed to find whether the most beneficial treatment for knee OA would be to use *C. longa* L. extract alone, or combined with conventional treatment.

Conclusion

Curcumin or *C. longa* L. extract may have therapeutic utility in the treatment of knee OA in humans. Curcumin seems to show benefits in pain relief and functionality of the knee joint. It seems to be equivalent in efficacy to the conventional knee OA treatment. Curcumin seems to have fewer adverse effects compared to conventional treatment with paracetamol or NSAIDs, since their chronic use could lead to gastrointestinal problems. Curcumin seems to have anti-inflammatory and anti-oxidative properties, which helps in reducing synovial biomarkers of inflammation caused by knee OA. Curcumin seems to have benefits when used alone or in combination with diclofenac. There is no consensus on the optimal dose of curcumin for the treatment of knee OA. Current research on the efficacy of turmeric as a treatment for knee OA, although promising, it does not allow us to draw firm conclusions. The number of randomized clinical trials are scarce, the existing ones have limitations and the results obtained are not unanimous.

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