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A Mini-Review of Curcumin Therapy in Pain Treatment

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Abstract

Introduction: *Pain is a significant, multifactorial problem worldwide. Curcumin, a derivative of the rhizome of turmeric (Curcuma longa), has been historically used in Asian medicine due to its anti-inflammatory and analgesic properties. Recent clinical trials have demonstrated its potential analgesic effect. This mini-review aimed to summarize the analgesic effect of curcumin in the literature.*

Methods: *The Medline (PubMed) and Cochrane Central Register of Controlled Trials databases were searched for articles published until Sep 15th, 2022. Randomized controlled trials (RCT) on the effect of oral curcumin on pain control in five different categories (1) arthritis, (2) muscle soreness, (3) abdominal pain, (4) oral pain, and (5) other types of pain were included. The risk of bias was assessed using the Cochrane risk-of-bias tool for randomized trials (RoB2) tool.*

Results: *Nineteen full-text articles were included in the study, and eight studies described osteoarthritis (OA) of the knee. All of them reported an effect of curcumin on knee OA pain reduction compared to a placebo or a similar effect to other pain medicines. The RoB assessment results in five studies with an overall low risk of bias and eight with a high risk. Results regarding other pain categories are inconclusive, with two studies showing no effect of curcumin.*

Discussion: *Within the limitations of this mini-review, curcumin has the potential to be an effective agent for treating pain, mainly when used to manage knee OA-related pain. However, further studies on the impact of curcumin, particularly in other pain categories, are needed.*

Introduction

Across all age groups, pain is a significant clinical, social, and financial burden, with 1% to over 60% reported estimates of monthly prevalence (Henschke et al., 2015).

Pain is an unpleasant sensory and emotional experience associated with or resembling that associated with actual or potential tissue damage (Niv & Kreitler, 2001).

Steroidal and nonsteroidal drugs (NSAIDs) are common management strategies for pain. However, most drugs are associated with side effects and the risk of misuse and dependence (Hoffman et al., 2019). Therefore, developing safe and effective alternatives to commonly used analgesics has become a clinical and social necessity.

Curcumin, a natural component obtained from the rhizome of turmeric (Curcuma longa), has historically been used in traditional Asian medicine, as it has been suggested to exhibit analgesic and anti-inflammatory effects. Previous studies on animal models have shown significant analgesic activity (Zhao et al., 2021). Curcumin has also been described

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to reduce osteoarthritis (OA)-related pain, having an effect similar to that of NSAID but with a safer side effect profile (Zeng et al., 2021).

In this mini-review, we aim to highlight the antinociceptive effects of curcumin on somatic, visceral, and neuropathic pain differ in the following categories: arthritis, muscle soreness, abdominal pain, oral pain, and other types of pain.

Materials and Methods

A comprehensive literature search was conducted using the following databases: Cochrane Central Register of Controlled Trials and MEDLINE (PubMed). It was performed for randomized controlled clinical trials (RCTs) published between the date of inception of the database and September 15th, 2022. The entire search terms for each database are listed in Table 1a-1b.

The first screening process consisted of two independent investigators screening the titles and abstracts according to the pre-specified eligibility criteria. Subsequently, secondary screening and quality assessment of the full text were performed by two investigators. If necessary, a third investigator was consulted to reach the final decision. Zotero software (Corporation for Digital Scholarship, USA) and Google Sheets online editor (Google Docs, Google LLC, CA, USA) were used for the screening process.

The inclusion criteria were as follows: (1) RCTs, (2) oral treatment with curcumin and its derivatives (monotherapy), (3) pain assessed using the pain scale as the primary outcome, (4) adults with acute and/or chronic pain as the population, and (5) full text available in English.

The quality was assessed using the Cochrane Risk of Bias Tool (RoB2) for randomized trials (Sterne et al., 2019).

Results

The search strategy yielded a total of 451 papers. After removing duplicates, the titles and abstracts of the papers were screened, followed by the full text (251 and 53, respectively). RCTs were included in this study (Figure 1).

The results were grouped into five categories of pain: (1) arthritis, (2) muscle soreness, (3) abdominal pain, (4) oral pain, and (5) other types of pain. The pain was assessed using different pain scales, including the visual analog scale (VAS), numeric rating scale (NRS), Western Ontario and McMaster Universities Arthritis Index (WOMAC), Knee Injury and Osteoarthritis Outcome Score (KOOS), and others (Table 2).

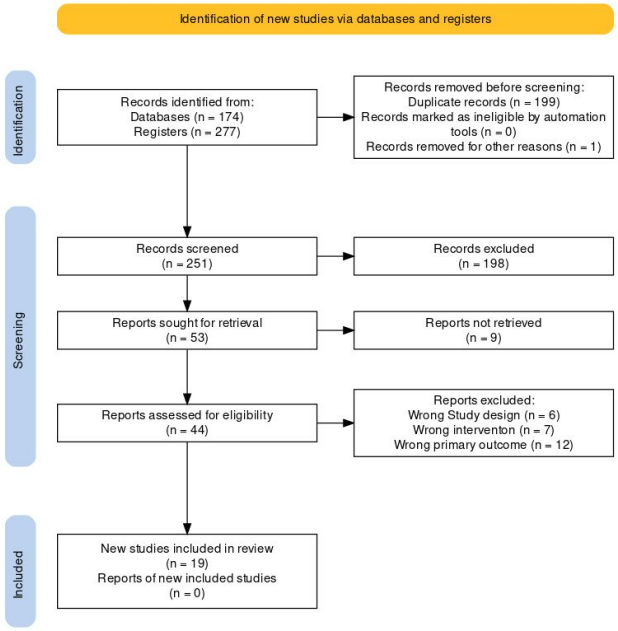

Figure 1: *Prisma Flow Diagram.*

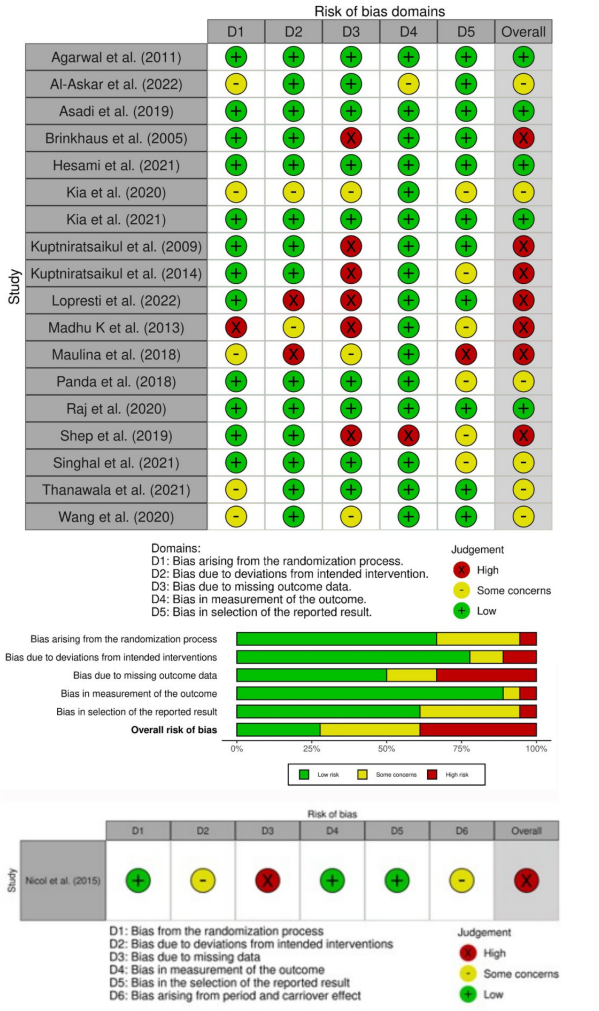

Figure 2: *2a.The risk of Bias in the studies included (parallel design); 2b.Risk of Bias in the studies included (crossover design).*

Figure 2a-2b summarizes the data using the Field risk-of-bias visualization (robvis) tool (McGuinness & Higgins, 2021). Eight of the assessed studies showed an overall high risk of bias, six some concerns, and five low risks of bias. The highest amount (7/19) of high-bias risk was related to bias due to missing data.

Arthritis

Ten studies describing the effects of curcumin on pain focus on its impact on joint pain and arthritis, with eight studies on knee OA.

Five studies evaluated curcumin in comparison with a placebo and found curcumin to be more effective, with a significant reduction in pain scores (Lopresti et al., 2021; Madhu et al., 2013; Panda et al., 2018; Raj et al., 2020; Thanawala et al., 2021). The KOSS pain scale, VAS, and WOMAC scores were used. Additionally, curcumin showed a good tolerance profile with adverse events that were not statistically different from the placebo, including abdominal pain, bloating, headache, and dyspepsia (Panda et al., 2018; Madhu et al., 2013). One trial by Wang et al. (2020) evaluated the effect of curcumin on knee symptoms and effusion synovitis of knee OA compared to placebo and observed a significant reduction in pain according to VAS, but it did not improve effusion synovitis.

Four non-inferiority studies compared the effects of curcumin on pain in knee OA with the standard of care, including ibuprofen, diclofenac, and paracetamol; (Kuptniratsaikul et al., 2009, 2014; Shep et al., 2019, S. 2019; Singhal et al., 2021). Two trials compared curcumin against ibuprofen, using the WOMAC pain scale, or pain improvement on walking and taking the stairs using NRS (Kuptniratsaikul et al., 2009, 2014). Non-inferiority of curcumin over ibuprofen was observed, and no difference between both for pain improvement on walking (Kuptniratsaikul et al., 2009, 2014). Additionally, there was no difference between the adverse events of Curcuma and ibuprofen (Kuptniratsaikul et al., 2009, 2014). Nevertheless, fewer side effects were associated with curcumin compared to diclofenac. Both treatments described a significant and similar reduction in the VAS pain score levels from baseline in OA of the knee (Shep et al., 2019).

Singhal et al. (2021) compared the efficacy and safety of curcumin extract with that of paracetamol. The analgesic effect of curcumin was non-inferior compared with that of paracetamol, according to the WOMAC pain scale, with fewer adverse events for curcumin.

Of the ten studies on knee OA and knee joint pain, only the study conducted by Raj et al. (2020) was assessed with an overall low risk of bias. Other nine studies showed overall high risk (5/10) or some concerns (4/10) of bias (Figure 2a).

#	Search Strategy for Cochrane Central Register of Controlled Trials Filtered for sources: Embase, PubMed, CINAHL
1	MeSH descriptor: [Pain] explode all trees
2	MeSH descriptor: [Curcuma] explode all trees
3	MeSH descriptor: [Curcumin] explode all trees
4	(curcum*)
5	(turmeric)
6	#2 OR #3 OR #4 OR #5
7	(pain*)
8	#1 OR #7
9	#6 AND #8

#	Search Strategy for PubMed (MEDLINE)
1	"Curcum*"[tw] OR "turmeric "[tw] OR "Curcumin"[Mesh] OR "Curcuma"[Mesh]
2	"Pain*"[tw] OR "Pain"[Mesh]
3	randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR clinical trials
4	as topic [mesh:noexp] OR randomly [tiab] OR trial [ti] "animals"[MeSH Terms] NOT "humans"[MeSH Terms]
5	#1 AND #2
6	#3 NOT #4
7	#5 AND #6

Table 1: *1a.Search strategy; 1b.Search strategy.*

Although the majority of the studies on arthritis or joint pain (8/10) are related to knee OA pain and show promising results for curcumin, there is still a need for high-quality studies with a low risk of bias and higher consistency to gain a general therapeutic recommendation.

Muscle soreness

One article describes the influence of curcumin on muscle soreness (Nicol et al., 2015), and the pain quality was assessed using the VAS scale.

Delayed-onset muscle soreness (DOMS) is discomfort or pain that follows unusual or intense eccentric exercise (Nicol et al., 2015). Nicol et al. (2015) reported a moderate to a significant reduction in pain (VAS) associated with DOMS in the curcumin group compared with the placebo group. These findings

First author (year)	Population and disease	Study Characteristics	Primary Outcome Measure (scale)	Experimental Intervention (preparation, type, dose, and duration)	Control Intervention (type, dose, and duration)	Main outcome results	Adverse effects (curcumin vs control)	Author's conclusions
Agarwal et al. (2011)	n=50 f=41, m=9 mean age 38.44 ± 12.7 years. Laparoscopic cholecystectomy	RCT, two arms, single-blinded, single center	Post-operative pain (VAS)	Curcumin 500mg 4x/day 3 weeks	Matching Placebo 500 mg 4x/day 3 weeks	VAS change CR 5±5.204; PL 30 ±13; p=0.000	No	CR improves postoperative pain
Al-Askar et al, (2022)	n=91 f=54, m=37 CR 58.4 ± 7.3; PL 57.2 ± 5.2 years Surgical periodontal therapy	RCT, two arms, single-blinded, single center	Post-operative pain (NRS)	Curcumin 400 mg 3x/day 3 days	Mefenamic acid 500 mg 3x/day 3 days	NRS No statistically significant difference	NS	Compared with MA, curcumin is ineffective for pain and discomfort management after SPT.
Asadi et al. (2019)	n=80 age 30-60 years old Non-insulin-dependent Diabetes Mellitus	RCT, double-blinded, placebo- controlled, single center	Sensorimotor (TCNS)	Nano-curcumin capsules 80 mg 1x/day 8 weeks	Placebo 1x/day 8 weeks	Neuropathy score (TCNS) CR −2.07(2.1); PL −0.60(1.5) p=0.3	2 cases of GI side effects	Improvement and reduction of severity of DSPN
Brinkhaus et al. (2005)	n=106 age 48±12 years IBS	RCT, triple arms, double-blinded, parallel, placebo -controlled, single center	IBS-related pain (VAS)	Curcuma xanthorrhiza 60 mg 3x/day 18 weeks	Placebo 3x/day or Fumitory 500mg 3x/day 18 weeks	VAS change CR +2.0±9.5; PL −0.3±9.9; Fumitory −0.9±11.5; p=0.81	No significant difference between arms regarding tolerability	No significant differences between groups
Gomes et al. (2021)	n=24 64±11.22 OA	RCT, triple arm, parallel, open-label, group trial, single center	VAS and WOMAC	Curcuma longa 500 mg 2x/day, 30 days	Miconia Albicans 500mg 2x/day Ibuprofen 1200mg/day	VAS reduction day 0: 7.25; day 30: 3.88; p=0.002	NS	Herbal medicine can interfere in the pain and function of patients with knee osteoarthritis
Hesami et al. (2021)	n=128 women CR: 22.11±2.09; PL: 23.19± 1.99; CR+ Mefenamic acid: 22.37 ± 2.41 Mefenamic acid: 23.01 ± 3.02 Healthy women	RCT, double-blinded, 2X2 factorial design	Dysmenorrhea (VAS)	Curcumin 500 mg Curcumin+ Mefenamic acid 500/250 mg Mefanic acid 250 mg 1x/day 5 days	Placebo 500mg 1x/day 5 days	VAS change CR 7.14±0.63 to 5.67±0.8; CR+ Mefenamic acid 7.35±0.75 to 4.86±0.1; Mefenamic acid 7.8±0.92 to 6.14±0.19 p=0.0392	NS	CR decrease pain, combination is more effective
Kia et al. (2021)	n=50 age 55.96±1.10 Post-radiation with/without head/neck cancer	RCT, double-blinded, placebo-controlled, single center	Oral mucositis (NRS)	Nano-micelle curcumin capsules, 80 mg 2x/day 7 weeks	Placebo 2x/day 7 weeks	NRS difference CR 5.28 ± 0.75; PL 6.16 ± 2.13 p≤ 0.001	NS	CR is effective in preventing radiotherapy- induced OM and decrease severity in pain compared to placebo
Kia et al. (2020)	n=57 CR 51.86±9.94; PL 53.67±8.90 years OLP	RCT, two arms, double-blinded, parallel, placebo-controlled, single center	OLP related pain (VAS)	Nano-curcumin capsule 80 mg 1x/day 4 weeks	Prednisolone 10 mg 1x/day 4 weeks	VAS change CR 2.69±2.89; PL 2.33±2.03 p≤ 0.001	NS	No significant differences between groups
Kuptniratsaikul et al. (2009)	n=107, CR 61.4±8.7; PL 60.0±8.4 years OA	RCT, two-arms single center	Knee pain on walking and on stairs (numerical rating scale)	Curcuma extracts 500mg 4x/day 6 weeks	Ibuprofen 400 mg 2x/day 6 weeks	Pain on level walking CR 2.7±2.6; IB 2.0±2.3; p=0.2 Pain on stairs CR 2.5±2.2; IB 2.5±2.60; p=0.92	No significant difference between arms, both GI tract mild AE	CR noninferior to IB in efficacy and safety for the treatment of knee OA
Kuptniratsaikul et al. (2014)	n=367 CR 60.3±6.8; IB 60.9±6.9 years OA	RCT, two-arms, double-blinded, active controlled, multicenter	Knee pain (WOMAC pain subscale)	Ethanolic extracts of turmeric - curcuminoids 75- 85% 1500 mg 1x/day 4 weeks	Ibuprofen 1200 mg/day 4 weeks	WOMAC pain CR 3.17±1.98; IB 3.25±2.11; p=0.018	Abdominal distention significantly higher in IB arm	CR noninferior to IB regarding pain control and functionality, w/ fewer GI side-effects for CR
Lopresti et al. (2022)	n=101 CR 59.59±0.92; PL 57.92±0.88 years OA	RCT, two-arms, double-blind, placebo- controlled, single-center	Knee pain (KOOS pain subscale)	Curcuminoids extract - curcuminoids 50% (Curcugen®) 500mg 2x/day 8 weeks	Placebo 2x/day 8 weeks	KOOS pain change CR 11.98 (7.38-16.59); PL 5.52 (0.75-10.28); p=0.009	No significant difference between arms	CR effective for pain compared to PL, but no changes in functionality scores
Madhu et al. (2013)	n=120 PL 56.77±9.98; CR 56.63±10.58 years OA	RCT, single-blind, parallel, placebo- controlled, single-center	Knee pain (VAS)	NR-INF-02 (extract from Curcuma longa Turmacin™) 500mg 2x/day 42 days	Placebo 400 mg 2x/day 42 days	VAS change CR 19.48±17.84; PL 46.03±20.84; p < 0.01	6.6% reported AE, all of them being dyspepsia	CR showed a statistically significant decrease in knee OA pain
Maulina et al. (2018)	n = 90 f=46, m=44 age 18-40 years Post-surgical removal of molars	RCT, double-blinded, parallel, single center	Oral pain (NRS)	500 mg amoxicillin + 200 mg curcumin capsule, 3x/day 24 hours	500 mg amoxicillin + 500 mg mefenamic acid 3x/day 24 hours	NRS reduction: 1st CR -2.31, PL -1.49; 2nd CR -4.11, PL -2.98; 3rd CR -5.87, PL -4.53; p=0.001	NS	Intervention group significantly less pain as control group
Nicol et al. (2015)	n=19 age 18–39 years Healthy men	RCT, double-blind randomized-controlled unilateral crossover trial, single center	Muscle Soreness (VAS)	Curcumin 2.5g 2x/day for 2.5 days prior to exercise, then 5 capsules 2x/day for 2.5 days after exercise	Placebo 2x/day 2.5 days prior to exercise, then 5 capsules 2x/day for 2.5 days after exercise	Single-leg Post-exercise baseline 0.9 ± 1.0; 24 h-baseline −0.5 ± 1.0; 48 h-baseline −0.8 ± 1.2; 24h post exercise −1.4 ± 1.0; 48 h-post-exercise −1.7 ± 1.0	No	CR supplementation prior to and following heavy eccentric exercise in healthy men lowered subsequent pain
Panda et al. (2018)	n=50 age 40-75 years OA	RCT, double- blinded, placebo-controlled, single center	Knee pain (WOMAC total score)	Curcuma extracts (Curene®) 500mg 1x/day	Placebo 1x/day	WOMAC pain CR -19.44±3.74; PL -6.6±3.66; p<0.05	No	Therapeutic efficacy and safety of CR over PL in the management of symptoms of OA
Raj et al. (2020)	n=90 Knee joint pain	RCT, triple arm, double-blind, placebo- controlled, single center	Knee pain (VAS)	Turmacin 1g 2x/day or 0.5g 2x/day 12 weeks	Placebo 2x/day 12 weeks	Pain scores CR 1g compared to PL -1.33±2.25; p=0.004; CR 0.5g vs PL -1.47±1.97; p<0.001	Heartburn in 4/90 (¼ in the PL group and ¼ in CR 1 g group)	CR (0.5 and 1 g) effective when compared to PL in increasing the pain threshold and knee ROM in healthy participants
Shep et al. (2019)	n=149 CR 53.09±4.17; DI 72.14±3.76 years OA	RCT, two-arms, open-labeled, active controlled, single center	Knee pain (VAS)	Curcumin BCM-95® - curcuminoids 95% 500mg 3x/day 28 days	Diclofenac sodium 50mg 2x/day 28 days	VAS change CR -5.93±0.99; p<0.01; DI -5.61±0.88; p<0.01	Fewer GI side effects CR group	CR similar to DI regarding pain relief, but better safety profile
Singhal et al. (2021)	n=144 f=107, m=37 CR 53.1 (10.9); PA: 50.8 (9.9) OA	RCT, two arms, single center, non-inferiority	Knee pain (WOMAC pain)	turmeric extract 500mg 2x/day 6 weeks	Paracetamol 650 mg 3x/day 6 weeks	WOMAC pain p=0.00004	5.48% (restlessness (4.11%), tingling sensation (1.37%))	CR noninferior to paracetamol in improving the physical function and alleviating pain and stiffness of OA
Thanawala et al. (2021)	n = 106 CR = 53 PL = 53 OA	RCT, double- blinded, placebo-controlled, multicenter	Knee pain (VAS)	WDTE60N (water-dispersible turmeric extract): 250mg/day, 90 days	Placebo capsules	VAS reduction CR -1.5±0.7; PL -0.6±0.8; p=0.0001	NS	CR capable of alleviating chronic knee pain.
Wang et al. (2020)	n=70 f=18, m=52 mean age 61.5 years SD CL 8.5 SD PL 8.8 OA	RCT, two arms, single center	Knee pain (VAS)	Curcuma extract 2 x 500-mg capsules per day, 12 weeks	Placebo 2x/day 12 weeks	VAS change CL -23 (-29.8 to -17.7) CR -14.6 (-20.8 to -8.5) p=0.039	No	Curcuma was more effective than placebo for knee pain but did not affect knee effusion-synovitis.

RCT, randomized controlled trial; OA, osteoarthritis; CR, curcumin; DI, diclofenac sodium; PA, paracetamol; IB, ibuprofen; KOOS, knee injury and osteoarthritis outcome score; VAS, visual analog scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; GI, gastro-intestinal; NRS, numeric rating scale, NS not stated, ORL oral lichen planus, RA, Rheumatoid Arthritis; IBS, Irritable bowel syndrome; AE, Adverse effect; m, male; f, female

Table 2: *Characteristics of the included studies.*

provided the first evidence that curcumin may be used to prevent and treat DOMS caused by strenuous exercise.

Curcumin intake seems to have an overall positive effect on muscle soreness; however, the study shows an overall high risk of bias. Further studies are needed in this field.

Abdominal pain

Hesami et al. (2021) showed a significant reduction in menstrual pain with curcumin compared with the placebo using VAS. This study showed an overall low risk of bias.

Furthermore, Brinkhaus et al. (2005) described using curcumin in irritable bowel syndrome (IBS). The authors used VAS to assess the pain related to IBS. The use of curcumin did not show any therapeutic benefit over the placebo. Nevertheless, the overall risk of bias was high for this study.

Further studies are needed to generalize the effects of curcumin on abdominal pain.

Oral pain

Four articles described the systematic use of curcumin for oral pain (Al-Askar et al., 2022; Kia et al., 2020, 2021; Maulina et al., 2018).

The treatment of oral lichen planus (OPL) with curcumin was described by Kia et al. (2020). The authors used VAS to assess the pain related to OPL. No significant differences were observed between the effects of curcumin and prednisolone.

Kia et al. (2021) assessed the effect of nanomicelle curcumin on the treatment and prevention of radiotherapy/chemotherapy-induced oral mucositis (OM). The results showed a better effect on OM severity and pain reduction in the chemotherapy-induced group than in the radiotherapy group.

Two studies evaluated treatment with curcumin after dental surgery.

Maulina et al. (2018) compared the effectiveness of pain treatment with curcumin with treatment with mefenamic acid after the surgical removal of impacted third molars. Treatment with curcumin significantly reduced pain, as assessed by NRS.

Al Askar et al. (2022) compared Curcuma longa's effects with mefenamic acid following periodontal surgery. The study was not blinded to the investigator. The participants took two capsules of curcumin but one capsule of mefenamic acid, which may have enabled the patients to identify their intervention group. There were no differences in the mean postoperative pain scores.

The study by Maulina et al. (2013) showed an overall high risk of bias, whereas Kia et al. (2021) showed an overall low risk.

Thus, curcumin can potentially treat oral pain of different origins; however, further high-quality studies are needed to support and generalize these findings.

Other types of pain

Two articles described the analgesic effectiveness of curcumin in diabetic sensorimotor polyneuropathy and postsurgical pain (Agarwal, 2011; Asadi et al., 2019).

Asadi et al. (2019) assessed the effects of nanocurcumin on diabetic sensorimotor polyneuropathy. However, no significant difference was found between the groups regarding foot pain.

Agarwal et al. (2011) evaluated the effects of curcumin on postoperative pain in patients undergoing laparoscopic surgery. The pain was significantly lower in the curcumin group than in the placebo group.

Both studies were assessed with a low risk of bias.

Discussion

This mini-review compiles 19 articles on the use of curcumin in different types of pain, categorized as follows: arthritis, muscle soreness, abdominal pain, oral pain, and other kinds of pain. Despite the high risk of bias in the evidence, the results suggest that curcumin may have a potential for use in pain management, especially in pain related to knee OA.

The most common pharmacological treatment for arthritis is NSAIDs, which have substantial limitations. Therefore, curcumin may be a novel treatment option for knee OA-related pain. These findings are similar to the conclusions drawn by Paultre et al. (2021).

However, because of the lack of low-risk bias studies on knee OA in our assessment, more studies with low-risk bias are needed to confirm and support these conclusions.

Within the data supporting the use of curcumin, most of the primary outcomes were based on pain scales, such as VAS and WOMAC, and showed favorable results in pain management.

However, this mini-review has limitations. Firstly, the comprehensive literature search yielded limited RCT that met the inclusion criteria. Secondly, the heterogeneity in pain scales used in the studies may affect the comparability of results. Lastly, most studies focused on the effects of curcumin on arthritis, with knee OA being the only one.

Compared with previous studies (Paultre et al., 2021), the lack of reporting on non-pharmacological

interventions makes it challenging to attribute the findings solely to curcumin.

Furthermore, the limited follow-up period does not allow for inference on the efficacy of curcumin therapy over a more extended period.

In conclusion, while the evidence for the effects of curcumin is growing, further high-quality studies with a low risk of bias are needed to understand its potential benefits and risks in pain treatment fully. However, the indicated improved safety profile of curcumin compared to NSAIDS makes it a promising alternative or supplementary therapy.

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Conflicts of Interest

The authors declare no conflict of interest.

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