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Original Article

EFFICACY AND SAFETY OF *CURCUMA LONGA* EXTRACT IN THE TREATMENT OF OSTEOARTHRITIS: A SYSTEMATIC REVIEW

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ABSTRACT

Objective: Osteoarthritis (OA) is a chronic disease caused by inflammation of the tissue and bony structure of the joint, which affects more than 235 million people worldwide. Due to the adverse effects caused by the long-term use of standard treatment of OA, the attempt to find natural remedies to treat chronic diseases continues to rise. *Curcuma longa* is known to have anti-inflammatory effects, which may impact the pathophysiology of OA. While many randomized controlled trials show the efficacy of *Curcuma longa* extract in the treatment of OA, there has been no comprehensive review of this evidence.

Methods: We systematically searched PubMed, Cochrane, Scopus, ProQuest, EBSCOhost, and ScienceDirect for randomized controlled trials that evaluated *Curcuma longa* extract (CE extract) vs. control (placebo or other therapy). Three trials were identified. Data were then extracted from the studies and summarized descriptively.

Results: Across all trials, *Curcuma longa* therapy was proven to reduce Visual Analog Scale (VAS) and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores significantly compared to the control group. Adverse effects were less likely to appear in patients treated with *Curcuma longa* extract compared to other groups.

Conclusion: CL extract is beneficial as an alternative medication for OA treatment, shown by the reduced scores of the Visual Analog Scale (VAS) and WOMAC in all studies we reviewed.

Keywords: Curcuma longa, Osteoarthritis, WOMAC, VAS

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INTRODUCTION

Osteoarthritis (OA), one of the most common types of arthritis, is a chronic disease caused by inflammation of the tissue and bony structures of the joint. This condition worsens over time and may lead to the decreased thickness of the articular cartilage, narrowing of the joint space, increased density of the subchondral bone, formulation of osteophytes, and thickening of the synovial membrane, hence resulting in disability and the complete breakdown of cartilage [1, 2].

In the United States, OA affects more than 27 million adults and is currently the leading cause of chronic disability [3]. The World Health Organization's Global Burden of Disease Study identifies OA as a major contributor to disability, which affects more than 235 million people worldwide [4]. In developing countries, including Asia, people tend to have longer life expectancies, and it is predicted that OA will double in the next two decades, from 6.8% in 2008 to 16.2% in 2040 [5]. In Indonesia, it is estimated that OA will occur in 15.5% of men and 12.7% of women in the later stages of life [6].

The consequence of OA is notable due to its common presentation in earlier age groups, particularly in younger women with obesity. Furthermore, the economic cost of OA is high due to its lengthy treatment and patients' reduced productivity. Individuals who experience limitations in their daily activities due to OA may lose their jobs, thus affecting their families [3].

Various options for OA treatments include pharmacological, non-pharmacological, and surgical interventions. Pharmacological agents are the most frequently used option, which include acetaminophen, NSAIDs (naproxen, salicylates, ibuprofen, selective COX2 inhibitor (celecoxib)), glucosamine (GS), chondroitin sulfate, capsaicin, intra-articular injections of hyaluronic acid, and steroids. The side effects of these analgesics vary from mild gastritis to gastric ulcers, bleeding, and perforation [7]. Moreover, prolonged use of NSAIDs has been reported to produce side effects that affect the kidneys and gastrointestinal system. Similarly, therapy using steroids is known to slow the repair process and worsen OA [8].

Thus, the identification of a different way to treat OA with fewer side effects is becoming more important. Medicinal plants have been long known to be an important source of bioactive compounds, which produce fewer side effects and can deliver a very high therapeutic index. Worldwide, herbal agents are being studied for their scientific parameters and ability to treat OA [8]. *Curcuma longa,* commonly known as turmeric, contains curcumin, des-curcumin and des-metoxycurcumin that is known to have potent antioxidant, anti-inflammation, antimicrobial, and anti-carcinogenic effects. This plant has been widely used in East Asia for more than 100 y. Curcumin works both directly and indirectly through genomic activity provided by pro-inflammatory (PI) cytokines [8]. An animal study conducted by Pinsornsak *et al.* [7] reported that curcumin works by down-regulating the activation of NF-kB, which inhibits inflammatory mediators that include cyclooxygenase-2 (COX-2), 5-Lipoxygenase (LOX), adhesive molecules, and MMPs. Also, curcumin has been shown to suppress many pro-inflammatory (PI) cytokines, such as interleukin (IL)-1, IL-8, and nitric oxide synthase (NOS) [9, 10]. A study conducted by Kuptniratsaikul *et al.* [9] found that curcumin also inhibited the secretion of collagenase, etalase, and hyaluronidase. Moreover, curcumin was found to inhibit the activation of free radical activated transcription factors, such as AP-1 and NF-kB, and reduced PI cytokines, such as tumor necrosis factor alpha, interleukin-1 beta, and interleukin-8.

Furthermore, curcumin also exhibits antioxidant properties in the inhibition of nitric oxide synthase (NOS) production [9]. A recent study has shown that curcumin affects inhibition in collagenase and

stromelysin expression at micromolar concentrations, which suggests its therapeutic potential for the treatment of arthritis [11]. This outcome is also supported by a clinical trial conducted by Srivastava *et al.*[8] that *Curcuma longa* showed a significant improvement in patients with OA by increasing their quality of life and decreasing their pain [8].

The evidence noted above proves the value of *Curcuma longa* as a potential therapy for OA. The objective of this research is to provide a systematic review of the current evidence regarding the clinical efficacy of *Curcuma longa* in treating people with OA.

MATERIALS AND METHODS

Eligibility criteria

This study reviews evidence from randomized controlled trials (RCT) that assess the efficacy and safety of orally-administered *Curcuma longa* extract (CL extract) in the treatment of OA patients. Improvements in the VAS and the WOMAC Scale were used to establish the clinical relevance of existing statistical tests, used to compare scores between the use of placebo and standard treatment of OA with CL extract, based on the reviewed articles. Patients reviewed in this systematic review were of any age, gender, race, and length of follow-up.

Search strategy

To answer our objective, we conducted a systematic review of the literature according to the PRISMA[12] guidelines. A comprehensive search was performed in September 2018 in which we searched the *PubMed*, *Cochrane Library*, *Scopus*, *EBSCOhost*, *ScienceDirect*, and *ProQuest* databases, using keywords related to OA and *Curcuma longa* without language restrictions. The following keywords were used in searches of all the databases mentioned above: "Curcuma longa AND osteoarthritis."

Selection of studies

The criteria for inclusion and exclusion were determined before the searches. We included RCTs that studied OA patients with treatment using CL extract compare to the control group, which use standard pharmacological treatment of OA (such as diclofenac, glucosamine, and ibuprofen) and placebo. Studies with relevant titles were then collected and screened. Studies found in more than one database were removed. Full-paper manuscripts were then studied, and those that were irrelevant were excluded. Three studies were included in the systematic review.

Data extraction

Selected studies were further studied, and relevant information was extracted. Relevant information included the following: (1) study design, (2) patient characteristics, (3) intervention regimens, (4) controls (placebo and standard treatment) regimens, (5) safety and adverse effect from the treatment, and (6) method used to analyze the results. The primary outcome of interest was the treatment efficacy of orally-administered CL extract, classified as improvements of the value of VAS and WOMAC, compared to the baseline. Secondary outcomes in this review included adverse events from the therapy.

Risk of bias assessment

For all the selected studies, a risk of bias assessment was conducted with *The Cochrane Risk of Bias Tool* [13], which allows assessors to judge the selected studies based on seven domains of bias. Any disagreements in the judgment of risk of bias were discussed and resolved between all authors before a final consensus was reached. Full details on our risk of bias assessment are described in the Results section and the Discussion.

RESULTS

Search results

The results of the search are shown in fig. 1. In the initial search, a total of 14 studies were acknowledged, of which ten were duplicates. However, after reading the full articles of the remaining studies, one study was excluded based on previously determined exclusion criteria. The remaining three studies were then selected as the final studies [7, 8, 10].

Study characteristics

Table 1 shows information regarding the patients' characteristics, inclusion, and exclusion criteria, regimes, control (placebo), and outcome measures from the three studies.

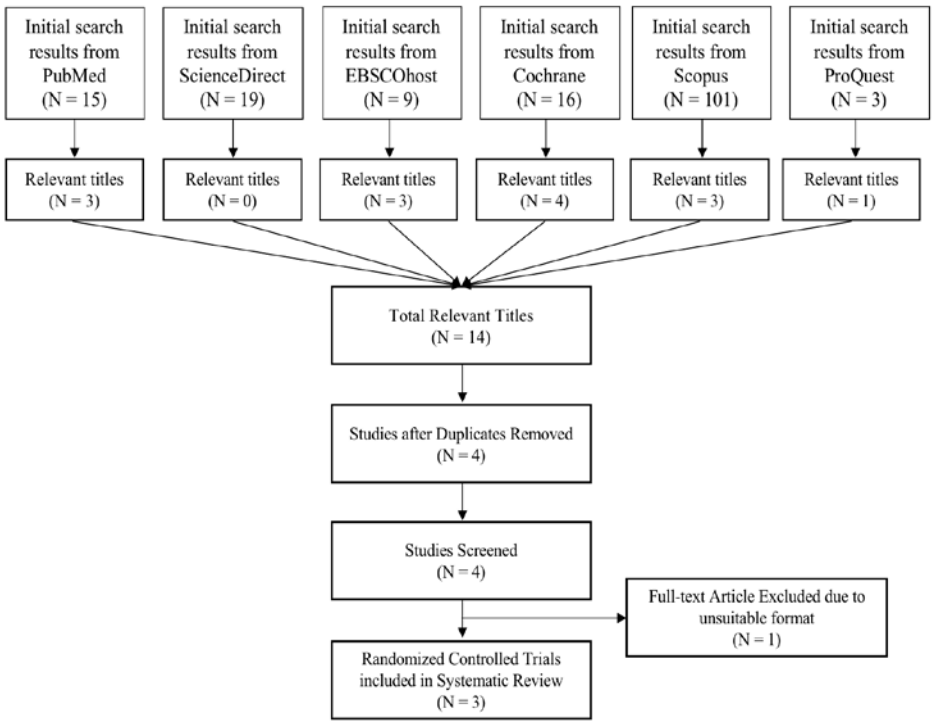

Fig. 1: Search results

Table 1: Summary of experimental designs of two studies

Study	Patient criteria and study design	Intervention and control	Outcome
Madhu, Chanda, and Saji (2013)	Age: >40 y (Mean age 56.8, 56.3, 56.8, 58.2 in control, NR-INF-02, GS, and NRF-INF-02 (CL extract)+GS groups respectively) Inclusion Criteria: Primary knee OA patients above 40 y Exclusion criteria: concurrent medical or arthritic conditions confounding the evaluation of knee OA, primary predominant patella-femoral disease, history of trauma/surgery in the affected knee, the coexisting disease that could preclude the completion of the trial Number of Patients: 120 (110 completed the full follow-up) Study Design: RCT (randomized placebo-controlled)	NR-INF-02, GS, NR-INF-02+GS, or Placebo for 42 d. Placebo 400 mg twice daily or NR-INF-02 500 mg twice daily or GS 750 mg twice daily alone or combination of NR-INF-02 and GS. Patients are not suggested to take other medication except for acetaminophen as a rescue medication	Outcome: VAS, WOMAC, CGIC, clinical assessment (joint tenderness, crepitation, effusion; terminal limitation of joint movement) at days 21 and 42 Adverse effects were found in all four groups. GS regimes had more adverse events than the other groups.
Srivastava, *et al.* (2016)	Age Range: 40-80 y (mean age 50.2 and 50.3 y in CL extract and control groups respectively) Inclusion Criteria: Primary knee OA patients (40-80 y) Exclusion Criteria: Less than 40 y or more than 80 y of age; patients who suffered from RA, DM, renal insufficiency, hepatic disease, cardiovascular disease, gout, or another ystematic disease; pregnant women Number of Patients: 160 (133 completed full follow-up) Study Design: RCT (two-arm double-blind, placebo-controlled parallel group)	CL extract or placebo for four months. CL extract 500 mg twice daily; placebo 500 mg capsule+diclofenac 50 mg/day twice daily.	Outcome: VAS, WOMAC, biomarkers parameter (IL-1β, ROS, MDA) at day 0, 60, and 120 Adverse effects were found in both groups; gastrointestinal problems, such as dyspepsia, nausea, and constipation
Pinsornsak and niempoog (2012)	Age Range: 38-80 y (30 subjects were 65-74 y) Inclusion Criteria: Patients with the history of knee pain with three of the following criteria: over 38 y old, less than 30 min of joint morning stiffness, crepitus on active motion, bony tenderness, bony enlargement, no palpable warmth of synovium would diagnose of OA Exclusion Criteria: Patients who were diagnosed with inflammatory arthritis (RA, gout, CPPD); patients who have the contraindication of using NSAID, history of peptic or gastric ulcer, renal insufficiency Number of Patients: 88 (75 completed full follow-up) Study Design: RCT (double-blind prospective RCT)	Curcuminoid capsules or placebo for three months. Placebo twice daily+diclofenac 25 mg three times daily; Curcuminoid capsules 250 mg twice daily+diclofenac 25 mg three times daily.	Outcome: VAS, KOOS (symptom, pain, function in daily living, function in sport and recreation, knee-related quality of life)

Table 2: Risk of bias assessment

	Domain of bias	Authors' assessment	Support for assessment
Madhu, Chanda, and Saji (2013)	Random Sequence Generation (Selection Bias)	Low Risk	Computer-generated randomization was applied
	Allocation Concealment (Selection Bias)	Low Risk	Both treatments had a similar appearance, prepared in "unique integer random numbers box containing either placebo or NR-INF-02 or combination" which both were given twice daily
	Blinding of Participants and Personnel (Performance Bias)	Unclear	Single-blinded study
	Blinding of Outcome Assessments (Detection Bias)	Low Risk	Not mentioned whether the outcome was measured blindly or not
	Incomplete Outcome Data (Attrition Bias)	Low Risk	High dropout numbers from all groups due to lost to follow-up, hence adequate sample size of 35 per group was not achieved
	Selective Reporting (Reporting Bias)	Unclear	Not mentioned whether all outcomes are reported
	Other Bias	High Risk	There was a disparity in the frequency of daily interventions between groups
Srivastava *et al.* (2016)	Random Sequence Generation (Selection Bias)	Low Risk	Computer-generated randomization was used
	Allocation Concealment (Selection Bias)	Unclear	Not mentioned
	Blinding of Participants and Personnel (Performance Bias)	Low Risk	Double-blinded study
	Blinding of Outcome Assessments (Detection Bias)	Unclear	Not mentioned
	Incomplete Outcome Data (Attrition Bias)	Unclear	Not mentioned
	Selective Reporting (Reporting Bias)	Low Risk	Although no strict reporting protocol was available, all expected outcomes of interest were reported
	Other Bias	Unclear	Not mentioned
Pinsornsak and Niempoog (2012)	Random Sequence Generation (Selection Bias)	Unclear	Not mentioned whether computerized randomization was used
	Allocation Concealment (Selection Bias)	Low risk	Both treatments had a similar appearance; the placebo is identical to the curcuminoid capsule
	Blinding of Participants and Personnel (Performance Bias)	Low Risk	Double-blinded study
	Blinding of Outcome Assessments (Detection Bias)	Unclear	Not mentioned whether the outcome was measured blindly
	Incomplete Outcome Data (Attrition Bias)	Low risk	High dropouts due to loss to follow-up and adverse events (control: renal dysfunction and allergy; intervention: hair loss)
	Selective Reporting (Reporting Bias)	Low Risk	Although no strict reporting protocol was available, all expected outcomes were reported
	Other Bias	Unclear	No evidence of bias from other sources

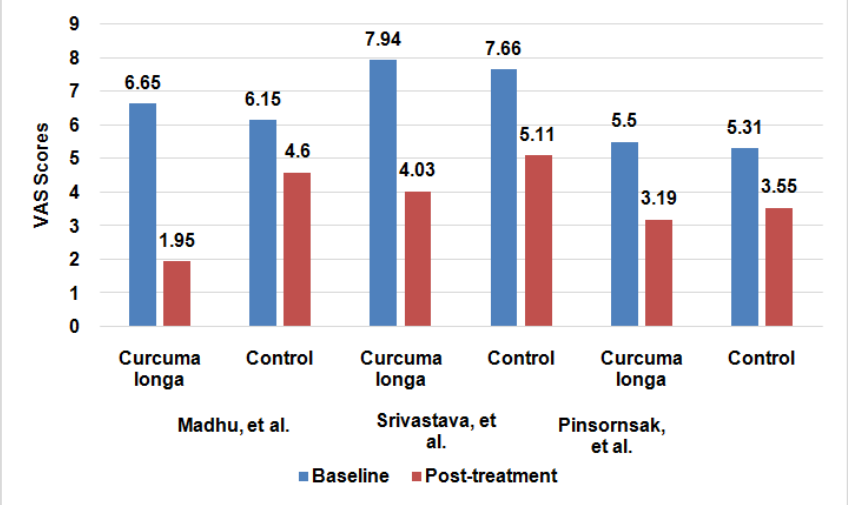

Fig. 2: Changes in VAS scores from baseline to post-treatment in intervention and control group

Risk of bias in selected studies

As mentioned above, the risk of bias assessment was conducted according to The Cochrane Collaboration's tool for assessing the risk of bias in randomized trials [14]. The collective judgments of the present study's authors are shown in table 2.

Outcome: changes in VAS and WOMAC

As the primary outcome, the data regarding changes in VAS and WOMAC were extracted from the selected studies. Synthesized data from the selected studies is represented in fig. 2.

In Madhu *et al.*'s study, [7] VAS scores decreased from a mean value of 66.50 to 19.48 in the intervention group (CL extract) with $p<0.05$, while the control group (placebo) only decreased from a mean value of 61.50 to 46.03, and the other control group (glucosamine [GS] as standard treatment) decreased from a mean value of 60.97 to 29.29 while the combination group (CL extract+GS) decreased from a mean value of 65.83 to 36.33.

In Srivastava *et al.*'s study,[8] there was a decrease in VAS scores, from a mean value of 7.94 to 4.03 in the intervention group (CL extract) with $p = 0.0001$, while the control group (placebo+diclofenac) decreased within a shorter range, from 7.66 to 5.11. In other hand, Pinsornsak *et al.*'study10 found that the VAS score decreased from a mean value of 5.50 to 3.19 in the intervention group (curcuminoid+diclofenac) with $p<0.001$), while the control group (placebo+diclofenac) decreased from a mean value of 5.31 to 3.55.

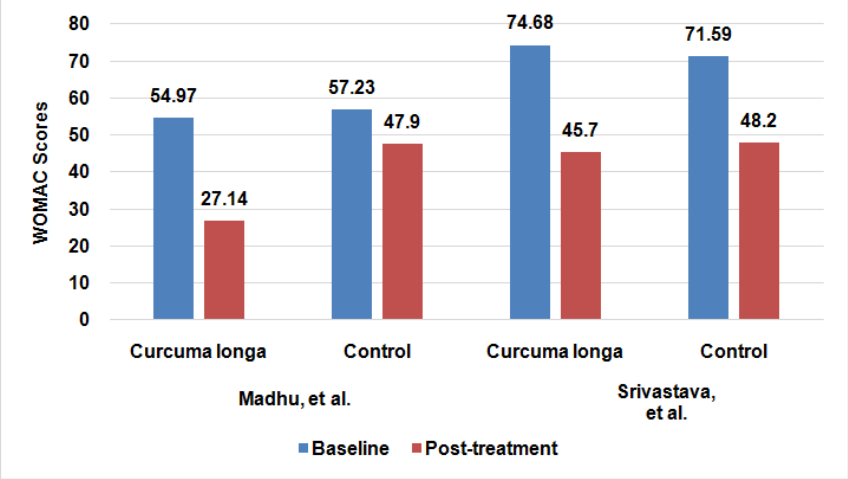

Fig. 3: WOMAC scores from baseline to post-treatment in intervention and control groups

Madhu *et al.* [7] found the WOMAC score decreased from a mean value of 54.97 to 27.14 in the intervention group ($p<0.05$) while in the control (placebo) group, the score decreased from a mean value of 57.23 to 47.90, the other control group (GS as standard treatment) decreased from a mean value of 58.30 to 34.92, and the combination group (CL extract+GS) decreased from a mean value of 60.73 to 36.21. Srivastava *et al.*[8] found the WOMAC score that evaluates pain decreased from a mean value of 15.10 to 9.48 in the intervention group ($p = 0.06$), while the control group decreased from a mean value of 15.29 to 10.16. The WOMAC score that evaluates stiffness decreased from a mean value of 5.55 to 4.08 in the intervention group ($p = 0.73$), while the control group decreased from a mean value of 5.31 to 4.16. The WOMAC score that evaluates function decreased from a mean value of 54.03 to 32.14 in the intervention group ($p = 0.008$), while its control decreased from a mean value of 50.99 to 33.88.

Outcome: safety of treatment

Side effects mentioned in the selected studies were collected to analyze the treatment's safety. Severe adverse effects were not

found in the three selected studies, and adverse effects mainly affected the gastrointestinal system. Madhu *et al.* [7] reported a total of 13 adverse effects, observed across all four groups. Subjects treated with CL extract exhibited the fewest number of events during the intervention period, while subjects who received GS exhibited the largest number of events. The adverse effects mentioned in all groups were mild and did not warrant the withdrawal of any study medication. The adverse events mentioned in Madhu *et al.*'s [7] study were generalized body pain, cough, dyspepsia, fever, sore throat, and pedal edema. Srivastava *et al.* [8] reported a total of six adverse effects, observed in both the intervention and control groups. Subjects who received the placebo reported more adverse events than subjects who received CL extract. The adverse events mentioned in Srivastava *et al.*'s study were dyspepsia, nausea/vomiting, and constipation. There were no side effects mentioned in Pinsornsak *et al.* [10].

DISCUSSION

Summary of evidence

The primary outcome of interest in this study is to identify improvements in the WOMAC and VAS scores from baseline to post-treatment in both the intervention and control groups. Two studies evaluated both WOMAC and VAS scores [7, 8], and one study evaluated only the VAS scores [10]. In all three trials, we found evidence that patients' pain decreased, as shown by the improvements in scores.

The VAS is an instrument designed to identify the characteristics of disease-related symptoms in individual patients. VAS is used to achieve rapid classification based on symptom severity. VAS has been widely used to measure pain intensity; it has also been used in a diverse population, including those with chronic diseases like OA [15, 16]. VAS is scaled from 0-10 with 0 described as no pain and 10 as the worst imaginable pain [16].

The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) is a questionnaire used to assess the health status of OA patients. WOMAC evaluates various aspects, including the patient's health and function. This questionnaire consists of 33 clinical symptoms (5 items), joint stiffness severity (2 items), pain severity (9 items), and daily life activity (17 items). Each item has five subscales where the best situation is described as "never" or "none" and the worst situation as "extreme" or "always". In this type of questionnaire, lesser scores represent a better situation (less pain) [17].

In the study by Madhu *et al.*, [7] there was a significant reduction in VAS scores: from 66.50±21.06 at baseline to 19.48±17.84 in the intervention group (CL extract) after 42 d of observation, with a $p<0.01$. There was also a significant reduction in VAS scores compared to placebo (61.50±13.71 at baseline to 46.03±20.84) and the combination of GS and CL treatment (65.83±15.48 at baseline to 36.33±28.99), with a $p<0.05$. Nonetheless, no significant difference was found between CL extract and GS treatment alone.

Unexpectedly, the effect of CL extract alone is superior compared to its combination with GS. Though unexplained, there may have been drug interactions that inhibited the combination therapy's efficacy.

Srivastava *et al.* [8] identified improvements in the VAS score, from 7.94±0.13 at baseline to 4.03±0.08 after 120 d of treatment with CL, with a $p<0.05$ compared to its controls (placebo 7.66±0.14 at baseline to 5.11±0.14).

In Pinsornsak *et al.*[10], both control (placebo) and CL extract-treated samples of the treatment were given diclofenac (NSAIDs). The VAS score fell from the mean of 5.50 at baseline to 3.19 after three months of observation in the group of samples that received CL extract and diclofenac, with a $p<0.001$. Reduction of scores was greater in the group that received both treatments (CL extract and diclofenac), yet when compared with the second group (5.31 at baseline to 3.55 at post-treatment), the distinction was not statistically significant.

Similarly, statistically significant improvements of WOMAC from baseline until post-treatment scores were reported [7], where the WOMAC score decreased from 54.97±9.85 at baseline to 27.14±16.13 after 42 d of observation with a p-value of<0.01 compared to its controls with $p<0.05$ (placebo 57.23±9.63 at baseline to 52.23±9.63). However, as with the VAS scores, there was no significant difference between the CL extract group and the GS group regarding the standard medication for OA (58.30±12.73 at baseline to 34.92±19.48). In Srivastava *et al.* [8], the WOMAC score included variables such as pain (11.19±0.26 and 9.48±0.17), stiffness (4.51±0.21 and 4.08±0.17), and PF (41.28±0.51 and 32.14±0.40) were also significantly ($p<0.05$) reduced in the treatment group than placebo group at day 60 and 120, if compared to the baseline.

It is worth mentioning a significant difference in improvement between the usage of CL extract in the studies by Srivastava *et al.* [8] and Pinsornsak *et al.* [10] Based on Perkins *et al.,*18 an increased dose of CL extract could improve the generalizability of results. Thus, the usage of 500 mg CL extract compared to 250 mg CL extract affects the overall improvement of VAS scores in patients with OA [18].

Madhu *et al.* [7] also assessed the use of acetaminophen (paracetamol) tablets in a dose range of 2,000 to 4,000 mg/day as rescue medication; this finding was reported as a secondary outcome measure, which was significantly less in the CL extract group compared to other groups ($p<0.01$).

Madhu *et al.* [7] also studied the Clinician Global Impression of change (CGIC) to assess improvement in patients' overall condition and evaluate the therapeutic efficacy. It is shown from his that there was a significant improvement in patients treated with CL extract. This effect may be considered as an additional parameter that supports CL extract's therapeutic efficacy [7].

In another study conducted by Pinsornsak *et al.* [10], using the Knee Injury and Osteoarthritis Outcome Score (KOOS) to evaluate short- and long-term symptoms and function of patients with a knee injury and OA, there was an improvement in all five aspects. The experimental group showed a superior or equal improvement at the end of the study, especially regarding pain and function in daily life. However, the control group had no statistically significant improvement ($p>0.05$) compared to the beginning of the study [10].

It is mentioned that there is a significantly raised level of Radical Oxygen Species (ROS) and Malondialdehyde (MDA) in patients with OA. The study by and Srivastava *et al.* [8] found that treatment with CL extract brought a decrease in baseline value of IL-1b, ROS, and MDA after two months of treatment. This decrease was further reduced as the treatment was continued up to four months. Therefore, this study found that CL extract can reduce biomarkers of inflammation [8].

Despite the evidence of overall improvement, as scored with VAS, WOMAC, CGIC, KOOS, it is known that radiological features correlate poorly with pain relief in OA. Madhu *et al.* [7] and Srivastava *et al.* [8] mention that the radiographic appearance of the joints was not improved, even after four months of treatment.

Limitations

This review is limited primarily by the scales used as the main outcome interest in the studies, which are both relatively subjective according to the patients' perspective of their pain. Another common limitation shown in these studies is a generally low sample size due to dropout during the follow-up process. Pinsornsak *et al.* [10] noted the limitation of an inadequate dose of curcumin given to subject groups since there were no previous studies evaluating the most effective regimen of CL extract in the treatment of OA in humans. Madhu *et al.* [*7*] reported an insufficient treatment duration, causing the inability to assess safety and efficacy for long-term management. Future research should focus on evaluating the effective treatment dosage of CL-extract in OA patients, from the perspectives of both efficacy and adverse events.

CONCLUSION

This review provides evidence that CL extract is beneficial as an alternative medication for OA treatment, shown by the reduce scores of VAS and WOMAC in all studies we reviewed. Adverse

effects occurred only in a few patients taking CL extract, with no serious adverse effect. We suggest the use of CL extract as an option of herbal treatment for OA.

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AUTHORS CONTRIBUTIONS

All the author have contributed equally

CONFLICT OF INTERES

There are no conflicts of interest to declare

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