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EFFICACY AND SAFETY OF CURCUMA LONGA EXTRACT IN PATIENTS WITH OSTEOARTHRITIS: A LITERATURE REVIEW

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ABSTRACT
Osteoarthritis (OA) is a chronic degenerative inflammatory disease that attacks the joints, especially the knee joints, in millions of people throughout the world. The main symptom of this disease is joint pain. Many studies have shown that components of *Curcuma longa* have beneficial effects in the pain management of OA patients. Objective to determine the efficacy and side effects of *Curcuma longa* in managing pain in patients suffering from osteoarthritis. Literature was created through various reference sources such as Pubmed, ScienceDirect, Google Scholar, and Epistemonikos which were screened against several inclusion criteria from 2013 - 2023. From the 277 articles obtained, 2 articles were obtained. *Curcuma longa* has been proven to significantly reduce pain scores according to VAS and WOMAC criteria. Apart from that, its effectiveness is not much different compared to non-steroidal anti-inflammatory drugs (NSAIDs). However, fewer side effects were reported in the *Curcuma longa* group. *Curcuma longa* can be used as a therapeutic option for mild to moderate osteoarthritis, especially in patients who cannot tolerate the side effects of NSAIDs.

Keywords: curcuma longa; osteoarthritis; pain

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INTRODUCTION

Osteoarthritis (OA) is a chronic degenerative and complex arthritic disease characterized by pain and decreased joint function. The prevalence of OA is approximately 240 million people worldwide with approximately 10% of men and 18% of women (Henrique et al., 2022; Hsiao et al., 2021). Although the prevalence of knee OA is high throughout the world, the cause of OA is still unknown, and there is no curative treatment for the underlying cause, of all Modern medicine to treat joint pain, there are several alternative medicines that can be used to treat OA such as *Curcuma longa* (Hsiao et al., 2021).

As an alternative treatment, *Curcuma longa* has anti-inflammatory and antioxidant potential and is also known in traditional medicine for arthritis (Dai et al., 2021; Mashhadi, 2021). Curcumin is the main compound that has anti-inflammatory potential in *Curcuma longa*,

because it has been proven to influence agents such as Collagenase, Elastase, Cyclooxygenase, and Hyaluronidase (Dai et al., 2021; Hsiao et al., 2021; Mashhadi, 2021).

One of the diseases most frequently carried out in research or clinical trials is OA, which is usually characterized by joint inflammation (Hsiao et al., 2021). Pain is one of the symptoms caused by OA. Parameters that are generally used in OA patients, namely: VAS (Visual Analog Scale), WOMAC Score (The Western Ontario and McMaster Universities) as well as assessing the side effects of *Curcuma longa* which may occur in both low and high doses with varying duration of use (Dai et al., 2021; Mashhadi, 2021). So the aim of this literature review is to determine the efficacy and side effects of *Curcuma longa* in managing pain in patients suffering from OA.

METHOD

In this literature review, various journals taken from databases such as Pubmed, ScienceDirect, Google Scholar, Epistemonikos were used. Journal searches using the keywords "Curcuma longa" OR "Turmeric" OR "Curcumin" AND "Osteoarthritis" AND "VAS Score" OR "Side Effect" OR "WOMAC" from 2013 - 2023, in English, fully accessible for free, have VAS and WOMAC as outcomes, and Randomized Control Trial. Then, we obtained 2 articles, of which 277 articles were screened.

The results of the initial search were then reviewed by reading the title and abstract to assess the relevance of the literature. The relevance of the studies was further reviewed by reading the full text and assessed based on compliance with the inclusion and exclusion criteria. The search results were reviewed by 5 authors and if there was disagreement between the authors it would be resolved by discussion.

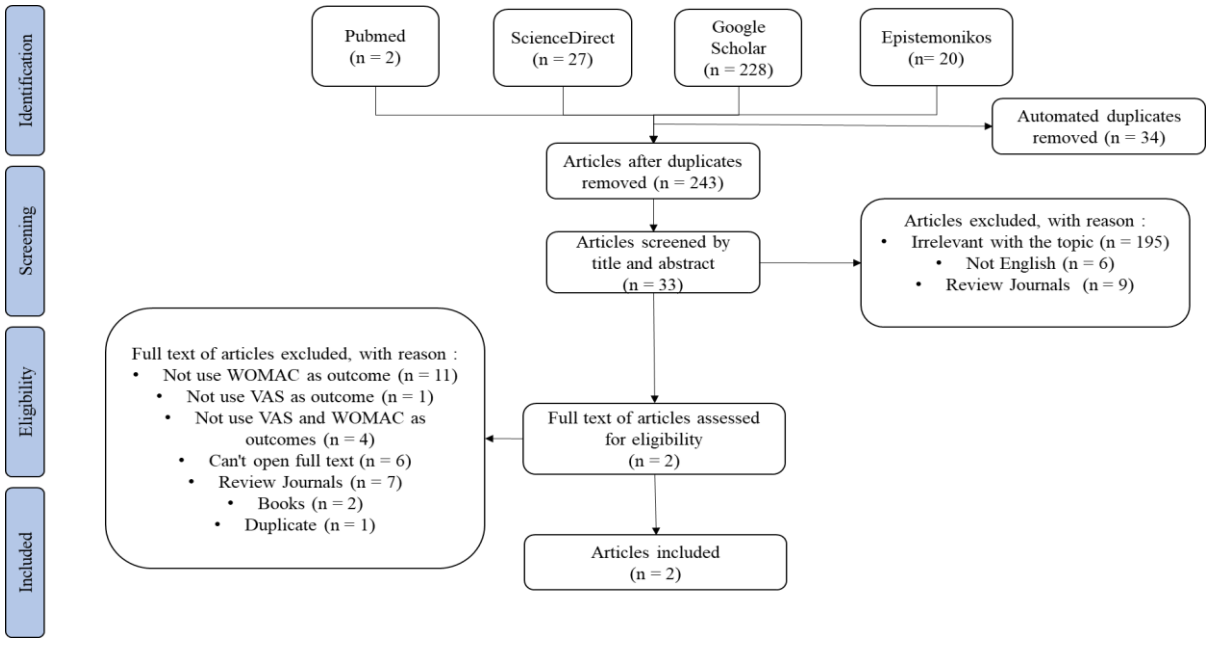

Figure 1. Flow Diagram for Journal Screening

RESULTS

Table 1.
Characteristic of The Articles

Researcher (Year)	Study Design	Sample Size	Intervention and Duration	Outcome
Gupte et al. (2019)	Randomized Controlled Trial	50 Participants randomly assign and divided into 2 groups: (Control: 27 Experimental: 23)	Participants divided into 2 groups: -Control Group: received Capsule Ibuprofen (400 mg) once in the morning followed by Placebo (dextrin) in the evening post meals for 90 days. -Experimental Group: received Longvida®, a Solid Lipid Curcumin Particles (SLCP) in the form of capsules twice daily (80 mg/capsule) post meals for 90 days.	1. Visual Analogue Scale (VAS): -Documented at baseline, days 7, 15, 45, 75, and 90. -There was significant decrease in VAS scores for both the groups from day 45 onwards as compared to baseline. -There was no significant difference between both the groups. 2. Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC): Calculated at baseline and days 30, 60, and 90. Gradual decrease was seen and statistically significant as compared to baseline scores in both the groups from day 60. There was no significant difference between both the groups. 3. Adverse Events: There were no serious adverse events reported in both the groups. In study group, two patients reported heartburn and nausea after taking the medicine. Both these patients dropped out from the study. One patient from the experimental group was withdrawn due to rash and itching all over the body after two doses of drug intake. The drug was de-challenged and re-challenged in this patient, but the symptoms reappeared. No significant changes in the blood and urine parameters were seen.
Sterzi et al. (2016)	Randomized Controlled Trial	53 Participants randomly assign and divided into 2 groups: (Control: 27 Experimental: 26)	All of participants in both groups received 20 sessions of physical therapy during the course of trial, throughout the whole study : -Control Group: received two placebo tablets per day for 8 weeks -Experimental Group: received two tablets of CartiJoint® forte (containing glucosamine hydrochloride, chondroitin sulfate, and Bio-Curcumin BCM-95®) per day The outcome was pain intensity measured by VAS and WOMAC, which assessed at baseline (t0), at 8 weeks (t1) and at 12 weeks (t2).	1. Visual Analogue Scale (VAS): -VAS at rest was found to be reduced between t0 and t1, as well as between t0 and t2 (p=0.0001), with no differences between groups (p=0.191). -VAS at motion revealed a significant "group × time-check" interaction (p=0.032), which underpins an increasing effect of time on VAS score reduction (p=0.0001) for both groups. -After 8 weeks, knee pain at motion for the experimental group appeared to be significantly reduced compared to the control group 2. Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC): -WOMAC scores showed a statistically significant reduction between t1 vs. t0 and t2 vs. t0 (p=0.0001) 3. Adverse Events: - No adverse events were reported during the study.

DISCUSSION

From the characteristics made in results, it can be seen that all articles show significant results on VAS and WOMAC scores, as well as minimal side effects (Gupte et al., 2019; Sterzi et al., 2016). Therefore, other research that has been carried out to support this data will be discussed further.

Definition and Pathophysiology of Osteoarthritis (OA) and *Curcuma longa*

Osteoarthritis (OA) is a chronic joint disease characterized by pain and decreased function of the joints. OA is caused by various disease pathways that cause joint damage. The pathophysiology of osteoarthritis is not completely understood, being caused by a variety of inflammatory and oxidative processes. The OA process starts from a decrease in healing function, joint aging, decreased cartilage function, environmental and genetic effects. Generally, increased cartilage degradation is caused by Matrix metalloproteinases (MMPs) and A disintegrin-like and Metalloproteinnase thrombospodin motifs (ADAMTS). There is an imbalance in the Extracellular Matrix (ECM) and Cartilage Degrading Enzyme components. Alarmins are also increased in OA, these molecules representing Damage-associated Molecular Patterns (DAMPs) have emerged which are cellular components of ECM degradation, which will bind to other cell membranes or intracellular receptors. DAMPs can bind to Toll-Like Receptors (TLRs), Activating inflammatory pathways and contributing to OA pathogenesis. The release of pro-inflammatory cytokines such as TNF-α, IL-1b and IL-6 causes the progression of OA to become increasingly severe, in addition to IL-8 and IL-18. Chondrocytes will experience apoptosis caused by oxidative stress and lysosomal dysfunction. Other inflammatory agents such as COX-2, Prostaglandin-2 released by synovial monocytes also influence the pathophysiology of OA (Henrique et al., 2022; Z. Wang et al., 2020).

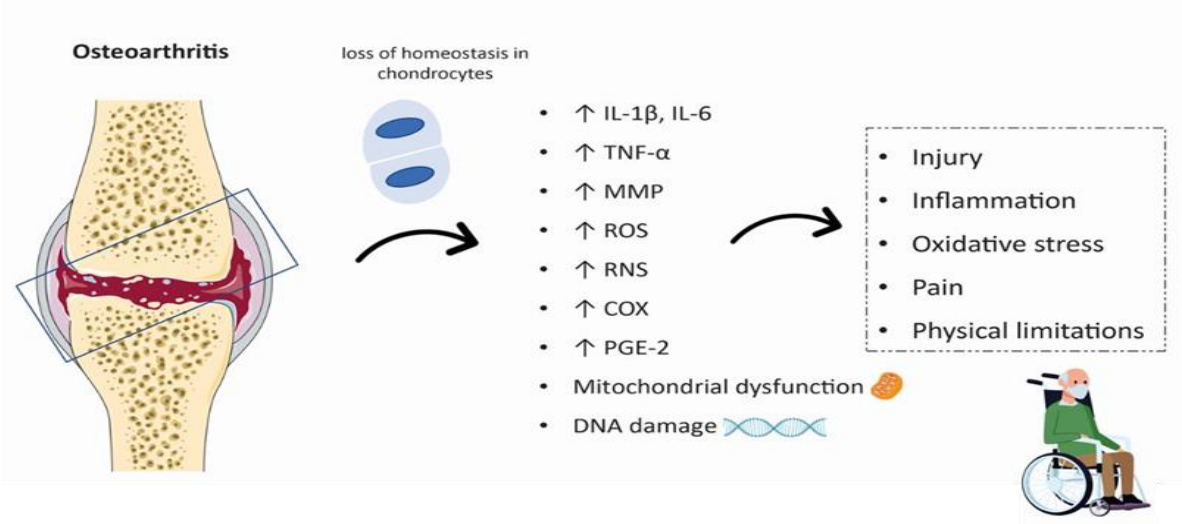

Figure 2. Osteoarthritis Pathophysiology (Henrique et al., 2022)

Curcuma longa, is a plant that has anti-inflammatory and antioxidant potential, as proven by various studies showing that *Curcuma longa* extract can modulate various biochemical pathways and modulate various molecular targets, including cytokines, enzymes, transcription factors and cell apoptosis. Curcumin, the main component of *Curcuma longa*, has been shown to influence various agents involved in inflammatory processes such as Collagenase, Elastase, Cyclooxygenase, and Hyaluronidase. Curcumin can also inhibit inflammatory mediators in the early onset of disease, having been shown to inhibit pro-inflammatory cytokines, including Tumor Necrosis Factor (TNF), Interleukin-1B (IL-1B), and IL-6). Curcumin has

been researched and is considered safe for consumption, even up to a dose of 8,000 mg/day for 3 months has been determined to be safe by the United States FDA (Food Drug Administration) (Dai et al., 2021; Mashhadi, 2021).

Based on a study by Shen, *et al*. It was found that the systemic bioavailability of curcumin was classified as poor (Shen et al., 2016). This was associated with the low stability of Curcuma longa extract in aqueous solutions at physiological pH. Thus, Curcuma longa extract will be degraded into trans-6-(4'-hydroxy-3'-methoxyphenyl)-2,4-dioxo-5-hexenal, ferulic aldehyde, ferulic acid, vanillin, vanillic acid, and other end products of dimerization (Heger et al., 2014). However, curcumin metabolites have anti-inflammatory and antioxidant activity that can reduce OA pain symptoms, therefore, to overcome the low absorption of curcumin and its rapid elimination from the body, various efforts have been made to increase the bioavailability of oral preparations such as through the use of piperine adjuvants, development curcumin-lecithin formulation, hydrophilic curcumin nanoparticle formulation, and coating curcumin with lipids or chitosan. However, it is also necessary to pay attention to the safety factor of using adjuvant therapy, for example piperine can increase bioavailability but involves very large risks so it requires close monitoring of patients because it increases the effect of absorption of other drugs/supplements and reduces drug metabolism in the liver (Cas & Ghidoni, 2019).

Relationship between *Curcuma longa* and OA

Curcuma longa is commonly used in cooking as a spice and in traditional medicine in Asia and India. *Curcuma longa* has three main components named curcumin, demethoxycurcumin, and bisdemethoxycurcumin. These three compounds are called curcuminoids. Curcumin is a natural polyphenolic compound that has low toxicity and is considered the main compound of rhizomes. Based on its pharmacological effects, curcumin and its analogues have been used in various studies involving several disease diagnoses such as cardiovascular disease, eye disease, diabetes, depression, HIV, vitiligo, Alzheimer's disease, endometriosis, osteoporosis, inflammatory bowel disease, epilepsy, Parkinson's disease, and cancer and also osteoarthritis (Akuri et al., 2017; Henrique et al., 2022; Hsiao et al., 2021). Studies on curcumin and its derivatives have confirmed their benefits in the treatment of OA. Studies show that in addition to improving symptoms in OA patients, curcumin may also help slow disease progression by reducing inflammation and cartilage damage and bone repair (Akuri et al., 2017; Dai et al., 2021; Mashhadi, 2021).

The biological effect of curcuminoid content is increasing the concentration of Superoxide Dismutase (SOD) and reducing the concentration of Glutathione (GSH) and Malondialdehyde (MDA), where curcuminoids have an effect on reducing oxidative stress in OA patients. *Curcuma longa* has biological effects, namely it can reduce pain, strengthen the patient's ability to walk further, improve joint lines, tenderness, and reduce crepitus. Where improvement in complaints is indicated by pain assessment or clinical examination without any side effects (better than celecoxib) (Akuri et al., 2017).

Effect of Using *Curcuma longa* in Osteoarthritis Patients with VAS Assessment

Pain is one of the symptoms caused by OA, while VAS (Visual Analogue Scale) is a valid, sensitive and easy to use tool for measuring the severity of pain. The VAS takes the form of a horizontal scale measuring 10 cm consisting of a score of 0 indicating no pain, a score of 1-2 indicating mild pain, a score of 4-6 indicating moderate pain, and a score of 7-10 indicating severe pain. In clinical trials the effectiveness of treatment can be measured more accurately using reduction pain intensity, namely the decrease in pain scores at the start and after therapy

(Daily et al., 2016; Shep et al., 2019; Yuan et al., 2022). Much literature shows the benefits of *Curcuma longa* for treating joint pain as indicated by improvements in VAS values. Wang, *et al.* conducted a study on knee OA patients with a VAS of at least 40 mm who were given *Curcuma longa* capsules 2 x 500 mg/day compared to placebo for 12 weeks, the VAS score improved more in the test group with a mean reduction of 23.8 mm and the placebo group 14.6 mm in at the end of the test, *Curcuma longa* reduced VAS by 9.1 mm (p=0.039) from placebo (Z. Wang et al., 2020). Nakagawa, *et al.* conducted a test on 50 knee OA patients with Kellgren–Lawrence grade II/III who were given 6 capsules each containing 180 mg curcumin for 8 weeks, resulting in a significantly higher improvement in VAS scores in the curcumin group compared to placebo at the end of the study (p=0.023), apart from that the need for celecoxib in each group was significantly smaller in the curcumin group compared to placebo (p=0.0252) (Nakagawa et al., 2014). Nakagawa, *et al*. conducted another test in the form of a prospective study, where 45 patients were given curcumin at the same dose and amount as in the previous study, the symptoms of knee pain were assessed for 6 months and the results showed that there was no significant decrease in VAS in the first month compared to the patient's initial condition (p=0, 1062) but starting from months 2 to 6 there was a significant decrease in VAS scores compared to baseline (Nakagawa et al., 2020).

Henrotin, *et al.* using bio-optimized *Curcuma longa* extract (BCL) FLEXOFYTOL® given 2x3 capsules/day for 84 days, the VAS value decreased on average by 22% (Henrotin et al., 2014). Henrotin, *et al.* (2019) re-used BCL FLEXOFYTOL® but with 2 different doses, namely a low dose of 2 x 2 capsules/day and a high dose of 2 x 3 capsules/day for 3 months, showing that VAS decreased significantly (p<0.001) at the low dose of BCL nor high, and there was no significant difference between the two BCL doses (p=0.9002) (Veronese, 2020). Meta-analysis Feng, *et al.* From the results of 11 studies totaling 870 patients, knee joint pain was assessed using VAS. All studies given CURs which is the main ingredient of *Curcuma longa* with varying doses and duration of administration compared to placebo showed greater benefits in improving knee pain VAS scores (p<0.001) (Feng et al., 2022). Meta-analysis research from Daily, *et al*. presented VAS results between the curcumin and placebo groups from three studies with significantly lower VAS results in the curcumin group compared to placebo (p<0.00001) (Daily et al., 2016). Meta-analysis research Zeng, *et al.* In line with previous results, 6 studies showed that *Curcuma longa* and curcumin could reduce VAS in knee OA sufferers (p<0.00001) (Zeng et al., 2021).

The use of *Curcuma longa* is not only an oral dosage form, studies from Jamali, *et al.* conducted a clinical trial using a 5% curcumin ointment preparation, which was made from a mixture of 95 grams of Vaseline and 5 grams of 90% dry curcumin extract powder, the ointment was applied 2 times a day for 6 weeks, at the end of the sixth week the average pain intensity was significantly lower in the 5% curcumin group compared to the placebo group (p=0.006) with a VAS difference between the two groups of 1.14 (11.4 mm on VAS) (Akuri et al., 2021). The benefits of *Curcuma longa* for relieving pain in OA patients are also widely compared to NSAIDs (non-steroidal anti-inflammatory drugs) as the first line of OA therapy (Akuri et al., 2021; Shep et al., 2019). Shep, *et al*. comparing 500 mg *Curcuma longa* extract gelatin capsules namely BCM-95® given 3x1 compared to 50 mg diclofenac tablets given 2x1 for 28 days. Both groups showed a significant decrease in VAS on day 28 (p<0.01) and there was no significant difference between groups. The number of patients experiencing a decrease in VAS scores of more than 50% was 66 people in the curcumin group and 67 people in the diclofenac group (Shep et al., 2019). Not up to there Shep, *et al.* conducted a clinical trial using a combination of BCM-95® capsules plus 50 mg diclofenac tablets both given simultaneously with a schedule of 2 times per day as a test group and a comparison of

50 mg diclofenac tablets given with a similar schedule for 28 days. Patients treated with curcumin plus diclofenac experienced a decrease pain intensity was significantly greater ($p<0.001$) on days 14 (3.73±0.83) and 28 (4.58±0.60) than diclofenac alone on day 14 (1.38± 0, 74) and 28 (2.20±0.61), the use of additional drugs such as paracetamol was significantly lower in the curcumin plus diclofenac group, namely 2 patients (3%) compared to the diclofenac group, namely 12 patients (17%) (Shep et al., 2020). Apart from diclofenac, there were also research using ibuprofen conducted by Yuan, *et al.* with 100 mg Cur capsules and 0.3 g ibuprofen extended-release tablets both given twice a day, the VAS scores of both groups decreased as the test progressed and after the intervention when compared the VAS of the two groups was not significantly different ($p>0.05$) (Yuan et al., 2022). Apart from medication, there is a lot of evidence that aerobic exercise such as walking and weight training is effective in reducing pain and improving muscle function. Shin, *et al.* conducted a test for 4 weeks on 25 patients who were divided into a group that received curcumin alone in the form of Theracurmin® at a dose of 3x700 mg and a group that received a similar dose of curcumin plus aerobic physical exercise in the form of 30 minutes of walking and weight training to strengthen the quadriceps femoris, hamstring, and triceps. The results were a significant decrease in VAS scores after 4 weeks in both groups ($p<0.001$), but there was no significant change in VAS if the two groups were compared at the end of the 4th week ($p=0.751$). This shows the intake of curcumin for 4 weeks with and without exercise. Physical therapy is effective in reducing pain (Shin et al., 2017).

Effects of Using *Curcuma longa* in Osteoarthritis Patients with WOMAC Assessment

The Western Ontario and Mc Master Universities Arthritis Index (WOMAC) is an index and score developed in 1982 at the University of Western Ontario and Mc Master. (1) This score has been widely applied in the field in clinical evaluation of Osteoarthritis. (2) This questionnaire divided into three main subscales, namely, pain assessment indicators which include five assessment points. The second indicator is an assessment of stiffness and the third indicator is an assessment of physical function which consists of 17 items (Ebrahimzadeh et al., 2014; Sathiyanarayanan et al., 2017).

WOMAC pain assessment at
Walking
Stair climbing
Night
Rest
Weight bearing
WOMAC stiffness assessment
In morning
Occurring during the day
WOMAC physical function assessment (difficulty for)
Descending stairs
Ascending stairs
Rising from sitting
Standing
Bending to the floor
Walking on flat
Getting in/out of a car
Going shopping
Putting on socks
Rising from bed
Taking off socks
Lying in bed
Getting in/out of bath
Sitting
Getting on/off toilet
Heavy domestic duties
Light domestic duties

Figure 3. Score Indicator for WOMAC (Puente et al., 2014)

The WOMAC score is often used as an indicator of the success of osteoarthritis treatment using *Curcuma longa* extract as a promising herbal therapy in improving the clinical features of patients with osteoarthritis. Research conducted by Zeng, *et al.* It was found that the extract from *Curcuma longa* can relieve pain which will result in improved WOMAC scores by improving joint function and reducing the incidence of stiffness in the joints. In this study it was also explained that the administration of *Curcuma longa* extract did not cause side effects when used, usually to achieve side effects it takes at least six weeks to use it and twelve weeks to achieve improvement in the WOMAC score (Zeng et al., 2021).

The results of other research conducted by Daily, *et al.* in the form of a meta-analysis study with the administration of 1000 mg/day of Curcuma longa for 8-12 weeks, it was found that of the five studies used, three studies showed significantly lower WOMAC scores in the group given therapy with Curcuma longa compared to placebo ($p=0.009$). In this study, it was also found that the WOMAC scores from these five studies showed that there was no significant difference between administering Curcuma longa and pain medication such as ibuprofen, diclofenac sodium, and glucosamine ($p=0.10$) (Daily et al., 2016). Research by Madhu, *et al*., to 120 research respondents, the administration of Curcuma longa 500 mg combined with the administration of chondroitin sulfate polysaccharide 750 mg twice a day (NR-INF-02) which was evaluated on days 21 and 42 was able to provide significant improvements in WOMAC scores ($p<0.05$) (Madhu et al., 2013).

According to research by Singhal, *et al.* administration of Curcuma longa extract with the product Curcugreen (BCM-95®) 500 mg capsules given twice a day to 73 patients with osteroarthritis compared to the control group who received paracetamol 650 mg therapy given three times a day to 71 control patients found that administration of the Curcugreen product

(BCM-95®) can reduce the WOMAC score of patients with osteoarthritis ($p<0.05$) for six weeks (Singhal et al., 2021). In addition, Curcugreen (BCM-95®) improves physical function and reduces pain and stiffness in patients suffering from osteoarthritis. In addition, pro-inflammatory cytokines in the form of CRP and TNF-α were significantly reduced in osteoarthritis patients. Meanwhile, patients receiving paracetamol therapy did not show an improvement in reducing pro-inflammatory cytokines, but it could reduce the WOMAC score of patients with osteoarthritis. Other research by Shin, *et al*. tested the effectiveness of the extract from Curcuma longa and its effect on the WOMAC score. The results of the research were the administration of Curcuma longa extract (Theracurmin®) 700 mg three times a day to 13 people and the combination of administering Theracurmin® 700 mg three times a day combined with 30 minutes of aerobic walking and weight training to increase leg muscle strength. quite relevant and significant results. Aerobic exercise starts at 15 minutes in the first week; then add five minutes every week so that in the last week the walking time reaches 30 minutes. Weight training consists of movements to strengthen the main muscles of the knee joint such as the quadriceps femoris, hamstrings, triceps and calf muscles. Testing was carried out for four weeks and the results showed that the WOMAC score decreased significantly in pain ($p<0.001$), decreased physical function impairment scores ($p<0.01$), and total score ($p<0.01$) in the group given the combination aerobic exercise therapy combined with Theracurmin®. In addition, in both research groups it was found that the patient's joint range of motion improved by measuring the range of motion (ROM) in the patient's active and passive joint flexion and extension positions (Shin et al., 2017).

Another research conducted by Panahi, *et al.* of 40 patients grouped into two groups, 19 people in the first group who received 1500 mg/day of *Curcuma longa* extract capsules in three doses showed a reduction in the burden of oxidative stress and reduced WOMAC scores. This extract from *Curcuma longa* is given together with piperine 15 mg/day which is able to increase the bioavailability of *Curcuma longa*'s performance in its pharmacokinetic processes in the human body. The combination of these two ingredients can increase the activity of SOD and reduced GSH and can reduce MDA levels compared to the placebo group, respectively, the average changes between the treatment groups and the respective controls were obtained ($p<0.001$); ($p=0.0064$), ($p=0.044$), changes in serum SOD activity, GSH concentration, and MDA during the experiment were significantly correlated. Short-term supplementation of curcuminoids can inhibit systemic oxidative stress in patients with osteoarthritis. The antioxidant effect is a therapeutic effect of curcuminoids which is reported to be able to produce good results on the patient's WOMAC score (Panahi et al., 2016).

Other research by Pinzon, *et al.* of 105 respondents who were divided into three groups, namely the group that received a combination of 350 mg of *Curcuma longa* extract with 150 mg of boswellia serrata, the group that received 350 mg of *Curcuma longa* extract alone, and the group that received a combination of 350 mg of *Curcuma longa* extract combined with administration NSAIDs. The three groups were assessed for WOMAC scores at the first and third visits. It was found that, the first and second groups were the groups that experienced a significant decrease in WOMAC scores ($p<0.001$) and the third group was the group that experienced the least reduction in WOMAC scores ($p<0.016$) (Pinzon & Wijaya, 2019).

Research that supports the results of previous research was also shown by Madhu, *et al*. on 40 osteoarthritis patients. Research respondents totaling 120 people with osteoarthritis were grouped into four groups, namely the first group received 400 mg of placebo taken twice a day, the second group received 500 mg of *Curcuma longa* polysaccharide extract (NR-INF-02) given twice a day, the third group received glucosamine sulfate 750 mg twice daily, and

the final group received a combination of NR-INF-02 and glucosamine sulfate for 42 days. A decrease in the severity of pain symptoms and knee function was seen from the WOMAC scores of each group. Analysis of post-treatment scores after administration of NR-INF-02 using WOMAC scores at each clinical visit showed a significant reduction ($p<0.05$) compared with placebo. So NR-INF-02 could be a candidate therapy option in patients with osteoarthritis (Madhu et al., 2013).

The results of research by Srivasatava, *et al.* also showed that 78 patients who received *Curcuma longa* extract 500 mg combined with diclofenac sodium 50 mg/day and 82 patients belonging to the control group received placebo 500 mg taken together with diclofenac sodium 50 mg/day for 4 months. Overall significant improvement was observed in the patient group given *Curcuma longa* extract 500 mg combined with diclofenac sodium 50 mg/day compared to the placebo group. Clinically, the WOMAC score became better, and simultaneously the levels of inflammatory biomarkers, namely IL-1β, ROS, and MDA, also decreased significantly ($p<0.05$) in the experimental group with 500 mg *Curcuma longa* extract combined with diclofenac sodium 50 mg/day (Srivastava et al., 2016).

Side Effects of Using Curcuma longa as an OA Treatment

Current management of Osteoarthritis (OA) relies on analgesics, NSAIDs, and corticosteroids, which can overcome pain and minimize inflammation, but these drugs have disadvantages in OA treatment, namely side effects, interactions, and drug contraindications. Possible side effects (ES) on the digestive, cardiovascular and renal systems limit the feasibility of administering long-term NSAIDs to patients (Srivastava et al., 2016). Therefore, exploration of alternative options with a good safety profile and outcomes for knee OA has been studied in traditional herbal medicine, one of which is *Curcuma longa*. Curcumin (diferuloylmethane) is a curcuminoid ingredient extracted from the roots of the *Curcuma longa* plant. Study by Liu, et. al. evaluating a large number of dietary supplements ranked curcumin as one of the most effective compounds for reducing OA pain in the short term and had less ES when compared with drugs commonly used in OA patients (Liu et al., 2018; J. Wang et al., 2017).

Adverse events were defined as undesirable events that occurred during treatment. Serious side effects were defined as unplanned hospital admission, new cancer diagnosis, or death during the study (Z. Wang et al., 2020). A study conducted by Feng, *et al*. found no significant difference in the incidence of side effects in the Curcuma longa group and the placebo group ($p= 0.745$). However, it was found that the incidence of ES was lower in the Curcuma longa group with main gastrointestinal symptoms such as meteorismus, gastroesophageal reflux, dyspepsia, nausea and abdominal pain (Feng et al., 2022). Another study conducted by Wang, et. al. showed that compared with placebo, Curcuma longa could significantly reduce knee pain over 12 weeks, as assessed by VAS and WOMAC, without an increase in side effects. In this study, no differences were found in the number of side effects reported between groups, which shows that Curcuma longa is safe and quite effective in treating osteoarthritis in this short-term study (J. Wang et al., 2017). This is supported by research conducted by Jamali, et. al. who reported that no patients experienced local or systemic side effects due to the use of curcumin (Jamadi et al., 2019). It has been proven that curcumin is safe and has minimal ES, observed from the research of Haroyan, et. al. where ES (nausea, vomiting, abdominal pain, gastroesophageal reflux, and flatulence) was observed in only 13 of 201 patients. The patients reported experiencing these side effects after being administered CuraMed® 500-mg capsules (333 mg curcuminoids) and Curamin® 500-mg capsules (350 mg curcuminoids and 150 mg boswellic acid) equally. Side effects occurred in

3% in the Curamin® group, 5% in the placebo group and 10.6% in the CuraMed® group. Analysis of the ES observed in the treatment and placebo groups explained that the type and frequency of side effects were found to be similar in all groups and may not be related to treatment. Severe ES was not observed (Haroyan et al., 2018). The above is supported by research by Lopresti, et. al. where there was a tendency for more side effects to be reported in the placebo group (n=10) compared to the curcumin group (n=5) including diarrhea, dyspepsia and abdominal pain. Additionally, there were no statistically significant differences between groups in changes in body weight (p=0.171), or systolic (p=0.772) and diastolic (p=0.900) blood pressure over time (Lopresti et al., 2022). There were significantly fewer patients in the curcumin group reported the occurrence of ES compared with the NSAID group. A good safety profile in the curcumin group was observed due to its gastroprotective and antiulcer effects, which may be an alternative to the GI side effects of NSAIDs (Shep et al., 2019).

CONCLUSION

Curcumin, as the main compound from *Curcuma longa*, can be used as a therapy for mild to moderate osteoarthritis based on various clinical trial studies that have been presented showing benefits in reducing pain symptoms suffered by patients due to its effect on inhibiting pro-inflammatory cytokines. Its use as single therapy or combination therapy with first-line osteoarthritis drugs, namely NSAIDs, shows that curcumin can improve patients' VAS and WOMAC scores in both low and high doses with varying duration of use and has minimal side effects compared to using NSAIDs in OA patients.

Curcuma longa in Indonesia itself is not yet a commonly used option in the therapy of osteoarthritis patients, therefore further studies are needed regarding the use of Curcuma longa in treating pain in OA patients related to bioavailability, optimal dose, duration of administration, impact of its use on other organs, as well as various effects side effects and toxicity that may arise, with the hope that in the future the use of Curcuma longa can be a therapeutic option for mild to moderate OA patients who cannot tolerate the side effects of NSAIDs.

REFERENCES

Akuri, M. C., Barbalho, S. M., Val, R. M., & Guiguer, E. L. (2017). *Reflections about Osteoarthritis and Curcuma longa*. 8–12. https://doi.org/10.4103/phrev.phrev

Akuri, M. C., Barbalho, S. M., Val, R. M., Guiguer, E. L., Hsiao, A., Lien, Y., Tzeng, I., Liu, C., Chou, S., Henrique, L., Martines, A., Marconato, G. G., Fracaro, G. G., Laurindo, L. F., Cressoni, A., Rubira, C. J., Dias, J. A., Sandra, M., Dai, W., … Akamatsu, S. (2021). Therapeutic Effects of Curcumin on Osteoarthritis and Its Protection of Chondrocytes Through the Wnt/B-Catenin Signaling Pathway. *Trials*, *22*(1), 1–12. https://doi.org/10.7326/M20-0990

Cas, M. D., & Ghidoni, R. (2019). Dietary curcumin: Correlation between bioavailability and health potential. *Nutrients*, *11*(9), 1–14. https://doi.org/10.3390/nu11092147

Dai, W., Yan, W., Chen, J., Hu, X., & Ao, Y. (2021). *Effectiveness of Curcuma longa extract versus placebo for the treatment of knee osteoarthritis : A systematic review and meta-analysis of randomized controlled trials*. *January*, 1–15. https://doi.org/10.1002/ptr.7204

Daily, J. W., Yang, M., & Park, S. (2016). Efficacy of Turmeric Extracts and Curcumin for

Alleviating the Symptoms of Joint Arthritis: A Systematic Review and Meta-Analysis of Randomized Clinical Trials. *Journal of Medicinal Food*, *19*(8), 717–729. https://doi.org/10.1089/jmf.2016.3705

Ebrahimzadeh, M. H., Makhmalbaf, H., Birjandinejad, A., Keshtan, F. G., Hoseini, H. A., & Mazloumi, S. M. (2014). *The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) in Persian Speaking Patients with Knee Osteoarthritis*. *57*(1), 57–62.

Feng, J., Li, Z., Tian, L., Mu, P., Hu, Y., Xiong, F., & Ma, X. (2022). Efficacy and safety of curcuminoids alone in alleviating pain and dysfunction for knee osteoarthritis: a systematic review and meta-analysis of randomized controlled trials. *BMC Complementary Medicine and Therapies*, *22*(1), 1–22. https://doi.org/10.1186/s12906-022-03740-9

Gupte, P. A., Giramkar, S. A., Harke, S. M., Kulkarni, S. K., Deshmukh, A. P., Hingorani, L. L., Mahajan, M. P., & Bhalerao, S. S. (2019). Evaluation of the efficacy and safety of capsule longvida® optimized curcumin (solid lipid curcumin particles) in knee osteoarthritis: A pilot clinical study. *Journal of Inflammation Research*, *12*, 145–152. https://doi.org/10.2147/JIR.S205390

Haroyan, A., Mukuchyan, V., Mkrtchyan, N., Minasyan, N., Gasparyan, S., Sargsyan, A., Narimanyan, M., & Hovhannisyan, A. (2018). Efficacy and safety of curcumin and its combination with boswellic acid in osteoarthritis: A comparative, randomized, double-blind, placebo-controlled study. *BMC Complementary and Alternative Medicine*, *18*(1), 1–16. https://doi.org/10.1186/s12906-017-2062-z

Heger, M., van Golen, R. F., Broekgaarden, M., & Michel, M. C. (2014). The molecular basis for the pharmacokinetics and pharmacodynamics of curcumin and its metabolites in relation to cancers. *Pharmacological Reviews*, *66*(1), 222–307. https://doi.org/10.1124/pr.110.004044

Henrique, L., Martines, A., Marconato, G. G., Fracaro, G. G., Laurindo, L. F., Cressoni, A., Rubira, C. J., Dias, J. A., & Sandra, M. (2022). *The Effects of Curcuma Longa on the Osteoarthritis : A Systematic Review of Placebo-Controlled Clinical Studies*. 1–17.

Henrotin, Y., Gharbi, M., Dierckxsens, Y., Priem, F., Marty, M., Seidel, L., Albert, A., Heuse, E., Bonnet, V., & Castermans, C. (2014). Decrease of a specific biomarker of collagen degradation in osteoarthritis, Coll2-1, by treatment with highly bioavailable curcumin during an exploratory clinical trial. *BMC Complementary and Alternative Medicine*, *14*. https://doi.org/10.1186/1472-6882-14-159

Hsiao, A. F., Lien, Y. C., Tzeng, I. S., Liu, C. T., Chou, S. H., & Horng, Y. S. (2021). The efficacy of high- and low-dose curcumin in knee osteoarthritis: A systematic review and meta-analysis. In *Complementary Therapies in Medicine* (Vol. 63, p. 102775). Elsevier Ltd. https://doi.org/10.1016/j.ctim.2021.102775

Jamadi, N., Adib-Hajbaghery, M., & Soleimani, A. (2019). The effect of Curcumin ointment on knee pain and quality of life in older adults with osteoarthritis. *BMC Complementary Medicine and Therapies*, *0*, 1–10.

Liu, X., Machado, G. C., Eyles, J. P., Ravi, V., & Hunter, D. J. (2018). Dietary supplements for treating osteoarthritis: A systematic review and meta-Analysis. *British Journal of*

Sports Medicine, *52*(3), 167–175. https://doi.org/10.1136/bjsports-2016-097333

Lopresti, A. L., Smith, S. J., Jackson-michel, S., & Fairchild, T. (2022). An investigation into the effects of a curcumin extract (Curcugen®) on osteoarthritis pain of the knee: A randomised, double-blind, placebo-controlled study. *Nutrients*, *14*(1). https://doi.org/10.3390/nu14010041

Madhu, K., Chanda, K., & Saji, M. J. (2013). Safety and efficacy of Curcuma longa extract in the treatment of painful knee osteoarthritis: A randomized placebo-controlled trial. *Inflammopharmacology*, *21*(2), 129–136. https://doi.org/10.1007/s10787-012-0163-3

Mashhadi. (2021). *A Systematic Review of the Clinical Use of Curcumin for the Treatment of Osteoarthritis*.

Nakagawa, Y., Mukai, S., Yamada, S., Matsuoka, M., Tarumi, E., Hashimoto, T., Tamura, C., Imaizumi, A., Nishihira, J., & Nakamura, T. (2014). Short-term effects of highly-bioavailable curcumin for treating knee osteoarthritis: a randomized, double-blind, placebo-controlled prospective study. *Journal of Orthopaedic Science*, *19*(6), 933–939. https://doi.org/10.1007/s00776-014-0633-0

Nakagawa, Y., Mukai, S., Yamada, S., Murata, S., Yabumoto, H., Maeda, T., & Akamatsu, S. (2020). The Efficacy and Safety of Highly-Bioavailable Curcumin for Treating Knee Osteoarthritis: A 6-Month Open-Labeled Prospective Study. *Clinical Medicine Insights: Arthritis and Musculoskeletal Disorders*, *13*. https://doi.org/10.1177/1179544120948471

Panahi, Y., Alishiri, G. H., Parvin, S., & Sahebkar, A. (2016). Mitigation of Systemic Oxidative Stress by Curcuminoids in Osteoarthritis: Results of a Randomized Controlled Trial. *Journal of Dietary Supplements*, *13*(2), 209–220. https://doi.org/10.3109/19390211.2015.1008611

Pinzon, R. T., & Wijaya, V. O. (2019). Curcuma longa and Boswellia serrata for Improving Functional Status in Osteoarthritis Patients: From Bench to Bedside Evidences. *Asian Journal of Medical Sciences*, *10*(5), 1–5. https://doi.org/10.3126/ajms.v10i5.24918

Puente, R., Illnait, J., Mas, R., Carbajal, D., Mendoza, S., Fernández, J. C., Mesa, M., Gámez, R., & Reyes, P. (2014). Evaluation of the effect of D-002, a mixture of beeswax alcohols, on osteoarthritis symptoms. *Korean Journal of Internal Medicine*, *29*(2), 191–202. https://doi.org/10.3904/kjim.2014.29.2.191

Sathiyanarayanan, S., Shankar, S., & Padmini, S. K. (2017). *Usefulness of WOMAC index as a screening tool for knee osteoarthritis among patients attending a rural health care center in Tamil Nadu*. *4*(11), 4290–4295.

Shen, L., Liu, C. C., An, C. Y., & Ji, H. F. (2016). How does curcumin work with poor bioavailability? Clues from experimental and theoretical studies. *Scientific Reports*, *6*(March 2015), 1–10. https://doi.org/10.1038/srep20872

Shep, D., Khanwelkar, C., Gade, P., & Karad, S. (2019). Safety and efficacy of curcumin versus diclofenac in knee osteoarthritis: A randomized open-label parallel-arm study. *Trials*, *20*(1). https://doi.org/10.1186/S13063-019-3327-2

Shep, D., Khanwelkar, C., Gade, P., Karad, S., & Zhang, Q. (2020). Efficacy and safety of combination of curcuminoid complex and diclofenac versus diclofenac in knee

osteoarthritis: A randomized trial. *Medicine (United States)*, *99*(16), E19723. https://doi.org/10.1097/MD.0000000000019723

Shin, Y. A., Suk, M. H., Jang, H. S., & Choi, H. J. (2017). Short-term effects of Theracurmin dose and exercise type on pain, walking ability, and muscle function in patients with knee osteoarthritis. *Journal of Exercise Rehabilitation*, *13*(6), 684–692. https://doi.org/10.12965/jer.1735064.532

Singhal, S., Hasan, N., Nirmal, K., Chawla, R., Chawla, S., Kalra, B. S., & Dhal, A. (2021). Bioavailable turmeric extract for knee osteoarthritis: a randomized, non-inferiority trial versus paracetamol. *Trials*, *22*(1), 1–11. https://doi.org/10.1186/s13063-021-05053-7

Srivastava, S., Saksena, A. K., Khattri, S., Kumar, S., & Dagur, R. S. (2016). Curcuma longa extract reduces inflammatory and oxidative stress biomarkers in osteoarthritis of knee: a four-month, double-blind, randomized, placebo-controlled trial. *Inflammopharmacology*, *24*(6), 377–388. https://doi.org/10.1007/s10787-016-0289-9

Sterzi, S., Giordani, L., Morrone, M., Lena, E., Magrone, G., Scarpini, C., Milighetti, S., Pellicciari, L., Bravi, M., Panni, I., Ljoka, C., Bressi, F., & Foti, C. (2016). The efficacy and safety of a combination of glucosamine hydrochloride, chondroitin sulfate and bio-curcumin with exercise in the treatment of knee osteoarthritis: A randomized, double-blind, placebo-controlled study. *European Journal of Physical and Rehabilitation Medicine*, *52*(3), 321–330.

Veronese, N. (2020). Reply to: "bio-optimized Curcuma longa extract is efficient on knee osteoarthritis pain: A double-blind multicenter randomized placebo controlled three-arm study." *Arthritis Research and Therapy*, *22*(1), 1–11. https://doi.org/10.1186/s13075-020-2107-4

Wang, J., Ma, J., Gu, J. H., Wang, F. Y., Shang, X. S., Tao, H. R., & Wang, X. (2017). Regulation of type II collagen, matrix metalloproteinase-13 and cell proliferation by interleukin-1β is mediated by curcumin via inhibition of NF-κB signaling in rat chondrocytes. *Molecular Medicine Reports*, *16*(2), 1837–1845. https://doi.org/10.3892/mmr.2017.6771

Wang, Z., Jones, G., Winzenberg, T., Cai, G., Laslett, L. L., Aitken, D., Hopper, I., Singh, A., Jones, R., Fripp, J., Ding, C., & Antony, B. (2020). Effectiveness of Curcuma longa Extract for the Treatment of Symptoms and Effusion-Synovitis of Knee Osteoarthritis : A Randomized Trial. *Annals of Internal Medicine*, *173*(11), 861–869. https://doi.org/10.7326/M20-0990

Yuan, T., Cai, D., Hu, B., Zhu, Y., & Qin, J. (2022). Therapeutic Effects of Curcumin on Osteoarthritis and Its Protection of Chondrocytes Through the Wnt/B-Catenin Signaling Pathway. *Alternative Therapies in Health and Medicine*, *28*(5), 28–37.

Zeng, L., Yu, G., Hao, W., Yang, K., & Chen, H. (2021). The efficacy and safety of Curcuma longa extract and curcumin supplements on osteoarthritis: A systematic review and meta-analysis. *Bioscience Reports*, *41*(6), 1–20. https://doi.org/10.1042/BSR20210817