Curcuma Extract as an Alternative and Safety Pain Reliever for Geriatric with Knee Osteoarthritis: A Systematic Review and Meta Analysis

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Keywords: Curcuma Extract, Osteoarthritis, Geriatric.

Abstract: Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) as pain relievers for osteoarthritis patients that have several side effects in long-term treatment. Meanwhile based on Global Burden of Disease 2019, about 528 million people have osteoarthritis, which 73% are geriatric patients. Therefore, this study aimed to evaluate the efficacy and safety of curcuma extract compared to NSAIDs in the treatment of geriatric patients with knee osteoarthritis. This study was made with a systematic literature search method from three databases, such as PubMed, ScienceDirect, and ProQuest. Inclusion criteria included experimental randomized control trials and discussed related topics. Mean difference and standard deviation were displayed as the results. With an I2 value of less than 40%, a fixed-effect model was suggested. For randomized trials, the Cochrane risk-of-bias tool was used to evaluate the risk of bias (RoB 2). There were a total of 671 participants in five randomized control trial trials. The pooled mean difference of the VAS score decreased significantly, with a 95% confidence interval (CI) of (-2.97) - (-0.92), P=0.0002, and an I2 of 99%. The I2 data for the KOOS index indicates 0%, and the pooled mean difference is a significant 2.82 [95% CI: 1.48-4.16, P<0.0001]. NSAID-like medications and curcuma extracts are similar in terms of effectiveness and safety.

1 INTRODUCTION

The most prevalent kind of arthritis worldwide is called osteoarthritis (OA), affecting around 528 million individuals, 73% of whom are elderly. (Global Burden of Disease Collaborative Network, 2019). More than half of OA patients experience knee pain, generally called knee osteoarthritis (KOA), which affects more than 300 million people around the world (Vos et al., 2016). Globally, the average yearly indirect expenditures per patient in 2013 were between $300 and $17,700 (Salmon et al., 2016). Meanwhile in Indonesia based on *Riset Kesehatan Dasar* (Riskesdas) in 2018, the prevalence of joint diseases including OA in the population over 15 years old was 7.3% and the percentage of people over 55 years old was 53.15% (Badan Penelitian dan Pengembangan Kesehatan Kementerian RI, 2018).

Multiple risk factors, mechanical stress, and abnormal joint movement combine to cause OA, an inflammatory disease that typically manifests as joint pain and loss of function. Articular cartilage changes lead to surface fibrillation, irregular cartilage, and focal erosion (Stewart & Kawcak, 2018). Although OA is not a deadly disease, previous studies showed that pain, stiffness, and physical abilities of patients with OA have impacted in decreasing their quality of life such as physical, social, and environmental health. The activities that were often reported as a problem were using the toilet, walking up the stairs, and heavy housework (Wojcieszek et al., 2022). Not only disrupted activities but also OA can impact mental issues like depressive disorders (Campbell et al., 2015). Currently, the drugs needed to eliminate OA are not available.

Therefore, therapies are needed that can manage symptoms, reduce disease progression, minimize disability, and improve quality of life. Available

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Wicaksono, M. S., Pravitha, C. A. and Daulay, H. R.
Curcuma Extract as an Alternative and Safety Pain Reliever for Geriatric with Knee Osteoarthritis: A Systematic Review and Meta Analysis.
DOI: 10.5220/0013666200003873

In *Proceedings of the 1st International Conference on Medical Science and Health (ICOMESH 2023)*, pages 69-77
ISBN: 978-989-758-740-5

therapies are pharmacological, non-pharmacological, and surgical therapies. For pharmacologic therapy, according to the IRA Recommendations for Osteoarthritis, the most common management of OA can be Analgesic Acetaminophen (paracetamol) and/or topical and oral NSAIDs (Perhimpunan Reumatologi Indonesia, 2014). Longterm use of NSAID drugs will have side effects on the development of gastric mucosal injury and induced nephrotoxicity including electrolyte imbalance such as hyperkalemia (Bindu et al., 2020; Wongrakpanich et al., 2018). Moreover, in the cardiovascular system, NSAIDs may be associated with increased blood pressure by 5 mmHg on average and risk of congestive heart failure (Wongrakpanich et al., 2018).

Currently, treatment with the concept of back to nature where the concept uses herbal ingredients is widely used by the Indonesian people, especially in elderly or geriatric patients. Turmeric (*Curcuma longa*), is a natural ingredient which very often used by Indonesians as an herbal treatment and as the main choice as an adjuvant pharmacological treatment. In addition to being cheap and easy to obtain, turmeric (*Curcuma longa*) has minimal side effects compared to pharmacological drugs (Mozaffari-Khosravi et al., 2016).

These natural ingredients can act as anti-inflammatories by inhibiting inflammatory mediators such as TNF-α, IL-1β, and PGE2 and reducing pain in OA patients (Heidari-Beni et al., 2020; Singhal et al., 2021). The mechanism of treatment with turmeric (*Curcuma longa*) has the same goal as pharmacological treatment, namely reducing symptoms in geriatric patients with OA. There is a main compound, curcumin, which is effective in managing pain in OA patients. The mechanism itself involves inhibiting the production of COX-2, phospholipase A2 (cPLA2), and 5-lipoxygenase (5-LOX); protection of IL-1β which causes chondrocyte apoptosis; and preventing cartilage degeneration in joints (Srivastava et al., 2016).

The purpose of this systematic review and meta-analysis is to examine the safety and efficacy of treating elderly people with osteoarthritis using natural components vs NSAIDs.

2 MATERIAL AND METHOD

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, which are available at (https://prisma-statement.org/), served as the foundation for this systematic review.

2.1 Eligibility Criteria

Eligible criteria included in this study were original research articles or research reports using human studies with randomized controlled trial design. Criteria for included studies were determined using PICO criteria shown in **Table 1**. Technical reports, editor answers, scientific posters, study protocols, conference abstracts, narrative reviews, systematic reviews, meta-analyses, non-comparative research, in silico, in vitro, and in vivo investigations were among the papers that were eliminated. Articles with non-English, unrelated themes, and full-text availability issues were also eliminated.

Table 1: PICO Criteria for Included Studies.

Population	Geriatric patients with knee osteoarthritis
Intervention	Curcuma extract consumed orally
Comparison	Placebo and NSAID
Outcome	Visual Analog Scale (VAS) and Knee Injury and Osteoarthritis Outcome Score (KOOS)

2.2 Outcome Measures

The Knee Injury and Osteoarthritis Outcome Score (KOOS) and Visual Analog Scale (VAS) pain ratings were the outcome measures evaluated in this systematic review and meta-analysis. Both scoring methods were applied to quantify the degree of discomfort associated with osteoarthritis in the knee.

Patients with osteoarthritis utilized the VAS score to gauge their level of knee discomfort. It has word descriptions in the range of 0 to 10 (in centimetres), where "0" denotes "no pain" and "10" denotes "unbearable or severe pain." The patient filled it out by checking the boxes for light, moderate, severe, and no discomfort. (Burckhardt & Dupree Jones, 2003).

KOOS is a self-assessment questionnaire designed to help people evaluate their own knee injuries. Five subscales make up the KOOS, and each is assessed independently: There are nine items related to pain; seven items to symptoms; seventeen items related to everyday living; five items related to sports and leisure; and four things related to quality of life. There are five alternative answers for each item, ranging from 0 (none) to 4 (severe). The results were converted to a 0-100 scale, where 0 denoted

very serious knee issues and 100 denoted no knee discomfort.

Table 2: Keyword Used in Literature Searching.

Database	Keywords
Pubmed	((((((curcuma[MeSH Major Topic]) OR (Curcuma longa[Title/Abstract])) OR (turmeric[Title/Abstract])) AND (geriatric[MeSH Major Topic])) AND (osteoarthritis[MeSH Major Topic])) OR (arthritis[Title/Abstract])) OR (degenerative[Title/Abstract])
ProQuest	(Curcuma OR (Curcuma longa) OR Turmeric AND (Osteoarthritis knee) AND Geriatric)
Science Direct	(Curcuma OR "Curcuma longa" OR Turmeric) AND (Geriatric) AND (Osteoarthritis OR Arthritis OR Degenerative)

2.3 Data Source and Search

Acquired studies have been collected using searching databases, such as PubMed, ProQuest, and Science Direct. The search was conducted from the inception of the database until December 2022. The keywords used were using Boolean operator and mesh in each database which can be seen in **Table 2**. The studies are stored in the authors' library using the Mendeley group reference manager.

2.4 Selection Process

After searching keywords written in **Table 2,** we used article type filters on each database to exclude the non-RCT articles. Results from 3 databases were later combined and screened by three independent reviewers through title, year of publication, and DOIs for duplicate removal. After duplicate removal, studies were later screened through abstract and full paper for irrelevance removal. The PRISMA flow chart contained records of the study selection procedures.

2.5 Data Collection Process

Studies after final screening are extracted for the relevant data and recorded in Google Spreadsheet. The recorded data were: (1) first author, year, (2) country, (3) sample size, (4) gender, (5) mean age, (6) name of intervention, length of intervention, comparison, and (7) outcome that consist of VAS score and KOOS index. All statistical tests for this meta-analysis were conducted using Review Manager (RevMan) v5.4 (Cochrane Collaboration, UK).

2.6 Study Risk of Bias Assessment (Quantitative Synthesis)

The Cochrane risk-of-bias tool for randomized trials (RoB 2), which is available at (https://methods.cochrane.org/bias/resources/rob-2-revised-cochrane-risk-bias-tool-randomized-trials), was used by three independent reviewers to evaluate each research that was included in this investigation. Later, the disparate conclusions made by reviewers were reviewed and settled among themselves.

2.7 Quantitative Data Synthesis (Meta-Analysis)

In this review, data on Mean Difference (MD) and Standard Deviation (SD) were computed. When the included studies were deemed homogeneous (little variability in study findings or variance owing to random error), as shown by an I2 value of less than 40%, a fixed-effect model (FEM) was applied. If not, a random-effect model (REM) was employed. A forest plot was used to display the pooled estimate.

3 RESULTS

3.1 Study Selection

After conducting literature searching from 3 databases which are PubMed, ProQuest, and ScienceDirect, 290.368 studies were generated. Automation tools from each database were used to exclude non-RCT studies, resulting in 282.254 articles being excluded. Then, 1.414 were removed due to duplicate articles. Later, authors assessed all of the remaining articles from the title and abstract for irrelevance to the topic, resulting in 6.669 articles excluded. 5 articles were then excluded for the unavailable full-text availability. Lastly, the author assessed eligibility for all the studies and agreed to exclude 17 studies because of an unpresent outcome of interest. Five papers were included in this study for the meta-analysis and systematic review. **Figure 1** shows the flow chart of the PRISMA diagram used to select our studies.

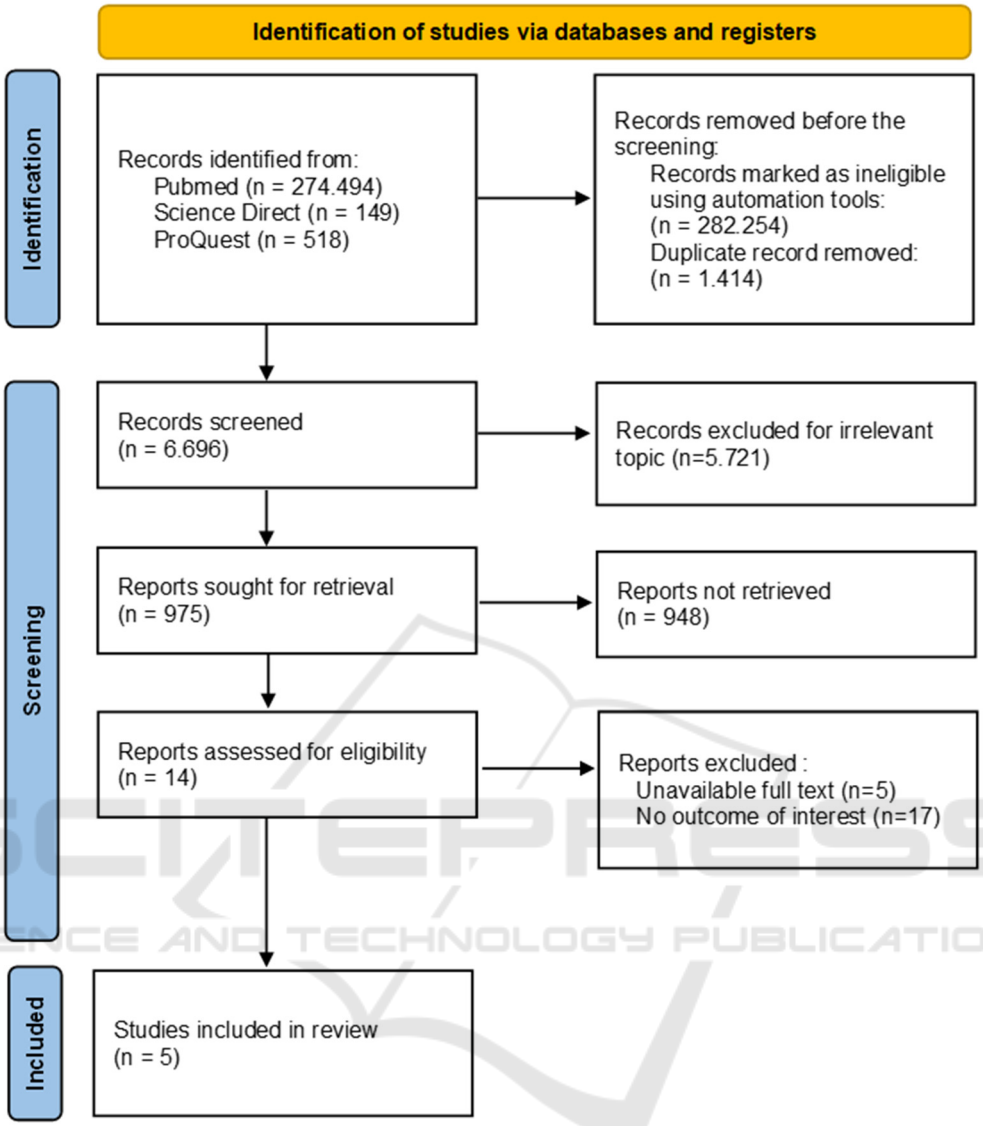

Figure 1: PRISMA 2020 Flow Diagram

3.2 Study Characteristic

From the five studies included in this review, the total number of participants is 671 participants. Most of the studies (n=5) observed the elderly participants for their studies, but only 1 study from Henrotin et al, researched geriatric (> 60-year-old) patients. The rest of the included studies were approached 60 years of age for their participants. The study characteristics are shown in **Table 3.**

3.3 Risk of Bias in Studies

To assess the quality of each study, the Cochrane risk-of-bias instrument for randomized trials (RoB 2) was utilized. One study showed a high risk of bias (Srivastava et al) because there is a bias due to the intended intervention being balanced between groups and missing outcome data causing participants lost to follow-up. Four studies showed some concern (Shep et al, Madhu et al. al, Henrontin et. al, Lopresti et. al) because there is an intended intervention as a rescue medication in each trial group. The risk of bias is summarized in **Figure 2.**

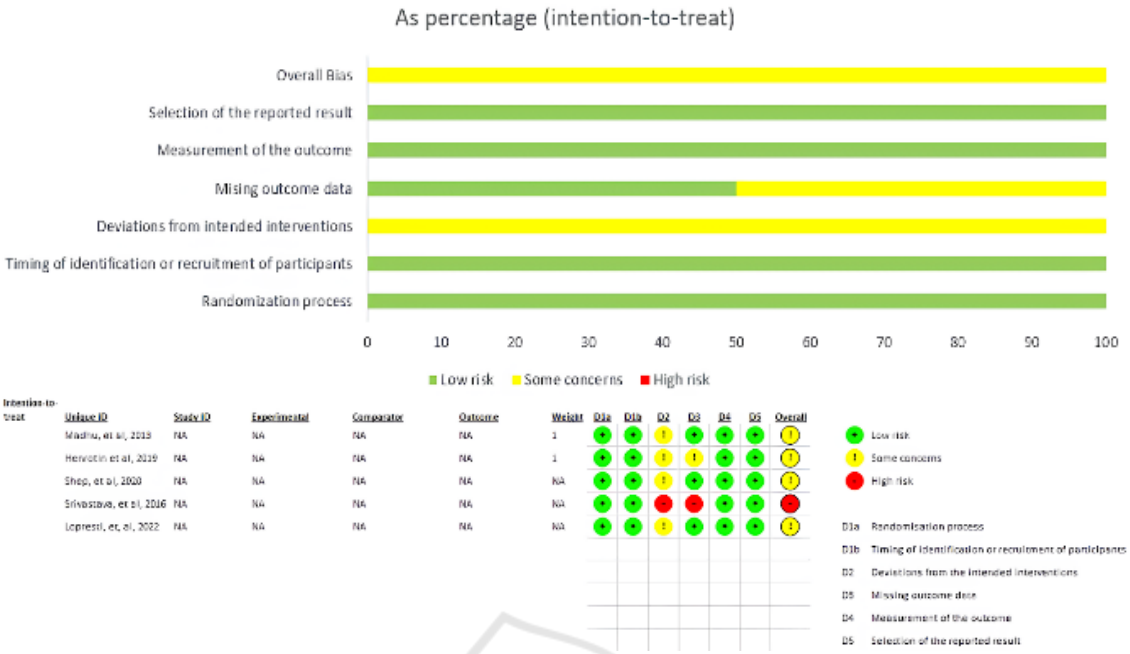

Figure 2: Risk of Bias Assessment Result

Table 3: Characteristic of Studies.

Author, Year		Madhu, et al, 2013[17]	Srivastava, et al, 2016[14]	Lopresti, et al. 2022[18]	Shep, et al, 2020[19]	Henrotin, et al. 2019[20]
Country		India	India	Australia	India	Belgium
Population	**Sample size**	120	160	101	140	150
	Sex	Female and Male	Female and Male	Female and Male	Female and Male	Female and Male
	Mean Age	57	50	58	52	60
Intervention	**Name of intervention**	1 capsule (500mg) curcuma extract	Curcuma extract 500mg/capsule with Diclofenac 50 mg/capsule	1 capsule (500 mg) curcumin extract	1 capsule (500 mg) curcuminoid complex (BCM-95) and 1 capsule (50 mg) diclofenac	Bio-optimised *Curcuma longa* (BCL) extract (500 mg/capsule)
	Length of intervention	42 days	4 months	2 months	28 days	3 months
	Comparison	1 capsule (400mg) Placebo (Microcrystalline cellulose)	Placebo 500mg/capsule with Diclofenac 50 mg/capsule	1 capsule (500mg) placebo	1 capsule (50 mg) Diclofenac	Placebo

Outcome	**VAS**	**Control**	Before = 6.15 ± 1.37 After = 4.60 ± 2.08	Before = 7.66 ± 0.14 After = 5.11 ± 0.14	N/A	Before = 7.81±0.73 After = 5.61±0.61	N/A
		Intervention	Before = 6.65 ± 2.1 After = 1.95 ± 1.78	Before = 7.94 ± 0.13 After = 4.03 ± 0.08	N/A	Before = 7.90±0.64 After = 3.32±0.60	N/A
		p-value	P < 0.05	P < 0.05	N/A	P < 0.001	N/A
	KOOS	**Control**	N/A	N/A	Before = 61.17 ± 13.65 After = 66.69 ± 16.66	Before = 51.58 ± 5.49 After = 90.38±3.61	Before = 44.2 ± 13.9 After = 55 ± 16.5
		Intervention	N/A	N/A	Before = 60.08 ± 12 After = 72.66 ± 16.77	Before = 53.15±4.24 After = 93.03 ± 4.75	Before = 45.8 ± 15.6 After = 58.6 ± 18.4
		p-value	N/A	N/A	P = 0.009	P < 0.001	P < 0.001
Abbreviation list		VAS, Visual Analog Scale; KOOS, Knee Injury and Osteoarthritis Outcome Score; N/A, not available					

3.4 Meta Analysis

Review Manager (RevMan) v5.4 (Cochrane Collaboration, UK) was used to conduct the statistical analysis. In this review, the Mean Difference (MD) and Standard Deviation (SD) were then computed with a 95% Confidence Interval (CI). The data was then processed into pooled standardized mean difference forest plot form. Our study assessed extractable quantitative data and grouped them into 2 outcomes which include VAS Score and KOOS Index. The forest plot of the meta-analysis can be seen in **Figure 3-4**.

A total of 5 studies with 671 participants of knee osteoarthritis patients, dominated by elderly patients >50 years old. Two included studies have VAS score outcomes, two included studies have KOOS index outcomes, and one study has VAS and KOOS outcomes that are analysed in this review.

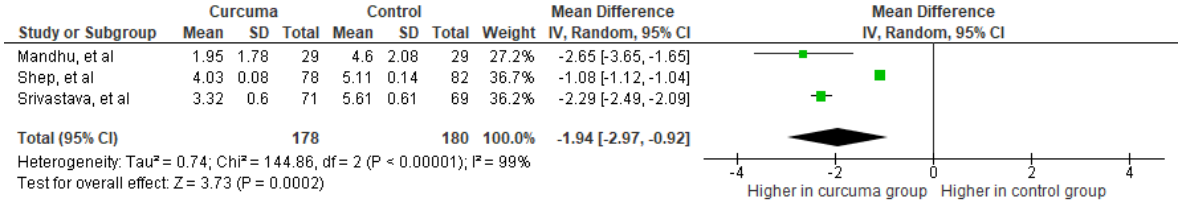

Figure 3: VAS Score.

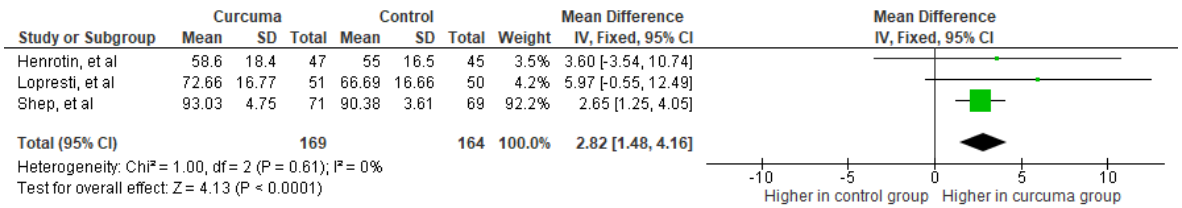

Figure 4: KOOS Index.

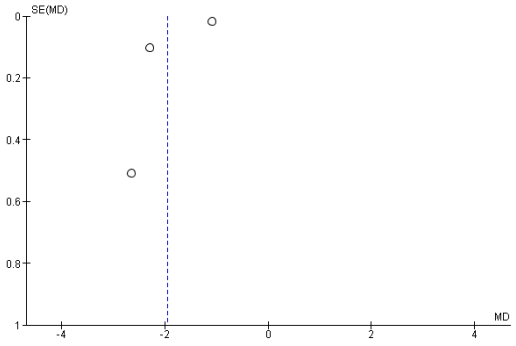

Figure 5: Funnel Plot of VAS Score.

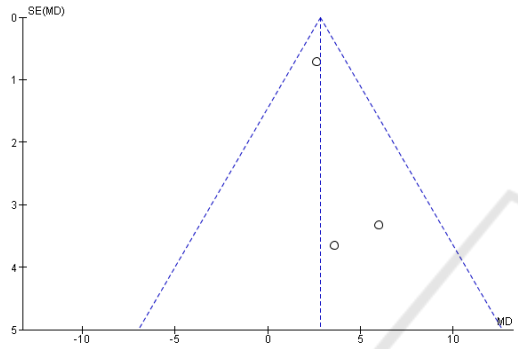

Figure 6: Funnel Plot of KOOS Index.

4 DISCUSSIONS

4.1 Curcuma Extract Improves Knee Pain on Knee Osteoarthritis

As a result of cartilage damage, osteoarthritis (OA) is an inflammatory disease that mostly manifests as joint discomfort and loss of joint function. Damage to the collagen matrix triggers chondrocyte proliferation and the production of hypertrophic chondrocyte cell clusters, which in turn promote the growth of ossified cartilage and the development of osteophytes (Stewart & Kawcak, 2018; Dobson et al., 2018; Loef et al., 2019). Increases in matrix metalloproteinase (MMP) and inflammatory cytokines like TNF-α and IL-1β are linked to this damage. Nitric oxide and reactive oxygen species (ROS) will rise as a result, leading to an increase in oxidative stress and worsening symptoms of joint inflammation (Sohn et al., 2012). Therefore, a treatment that acts as a good anti-inflammatory and antioxidant is needed to reduce pain and inflammation in geriatric patients with OA.

Curcuma extract has been shown to improve knee pain using VAS score on geriatric patients with knee osteoarthritis with a significant pooled mean difference (MD) of -1.94 [95% CI: (-2.97) - (-0.92), P = 0.0002] with I^2 showing 99%. Heterogenous results because there are 2 studies from Srivastava et al. and Shep et al. that use Diclofenac in both groups can produce biased results. Different formulations for curcuma extract also can induce bias in the study. Furthermore, curcuma extract has been shown to improve knee pain using the KOOS index with a significant pooled mean difference (MD) of 2.82 [95% CI: 1.48 - 4.16, P<0.0001] with I^2 showing 0%.

The components of curcuma extract include phenolic pigments (which contain the active ingredient curcumin, which acts as an anti-inflammatory agent), essential oils (such as cineole, linalool, α-terpinene, caryophyllene, ar-curcumene, zingiberen, curcumol, DL-turmerone, arturmerone, and dehydrocurdione), cholesterol, fatty acids, potassium, sodium, magnesium, calcium, manganese, iron, copper, and zinc, among other elements) (Karlowicz-Bodalska et al., 2017). The pain improvement in knee osteoarthritis was facilitated by the anti-inflammatory of curcuma extract that inhibits TNF-α, IL-1β, and PGE2. Curcumin, the main ingredient in curcuma extract, can reduce pain by inhibiting the production of COX-2 which produces the pain sensation (Srivastava et al., 2016).

The combination of curcuma and other NSAID medication can improve better outcomes compared with NSAID alone. Studies are being conducted to assess if curcuma extract is more effective as an adjuvant treatment for OA-related pain than NSAIDs alone. As seen from the VAS score data before and after treatment, the intervention group receiving a combination of curcuma and NSAID has a lower VAS score after treatment than just giving the NSAID alone (Shep et al., 2020; Srivastava et al., 2016).

4.2 Safety of Curcuma Extract

In some studies, curcuma extract has fewer adverse effects, such as dyspepsia, diarrhea, other gastrointestinal symptoms, and musculoskeletal symptoms compared to the placebo (Srivastava et al., 2016; Wang et al., 2020). In some OA cases, 6.6% of patients treated with curcuma exhibited the least number of adverse effects during the intervention period (Madhu et al., 2013). When curcuminoid complex is added to diclofenac as an adjuvant treatment, it helps to lessen the GI adverse effects caused by the drug and lessens the need for H2 blockers (Lopresti et al., 2021).

Curcuma extract as an alternative to NSAIDs in patients with osteoarthritis which mostly has adverse

effects that are mild and transient (Lopresti et al., 2021). From a pharmacological perspective, curcumin is a full choleretic-cholagamic agent. Because they compress the gallbladder, the curcumin cleavage products (ferulic and hydrofluoric acids) have cholecystokinin characteristics. On the other hand, paratholil methyl carbinol, another major component, has potent choleretic action. The choleretic action of curcumin causes a 62% rise in bile output (Shep et al., 2020). Despite the negative effects of curcumin extract, blood reports for liver, kidney, and complete blood counts did not significantly alter before or after the research drugs were taken (Henrotin et al., 2019).

4.3 Strengths and Limitations

The effectiveness of curcuma extract on elderly individuals with osteoarthritis in the knee is the subject of the first systematic review and meta-analysis conducted on this subject. This systematic review assessed the curcuma therapy effect that were consumed orally to reduce osteoarthritis pain in the elderly age. All studies included are randomized controlled trials with significant results in pain score by VAS score and KOOS index.

Nonetheless, this study is not without limitations. The studies that were included have a high and moderate risk of bias. The heterogeneity in the included studies is the different formulations but still given orally. Also, the use of other medications combined with curcuma extract, such as NSAID, can cause bias in the study result. Study duration can be the limitation of included studies because curcuma can't work significantly in a short time duration. Other factors, such as the severity and type of osteoarthritis are not discussed in including studies. There might be a possibility of missing some important information in studies written in other languages than English or Indonesian. Irretrievable full-text is also the limitation of this study. We suggest conducting more randomized control studies with a bigger sample size to notice more about the safety and efficacy of curcuma extract therapy and to optimize the impact of curcuma extract.

5 CONCLUSIONS

The use of curcuma extract is a potential treatment for knee osteoarthritis in elderly people, according to this systematic review and meta-analysis. It has been shown that curcuma extract is quantitatively significant in improving knee pain in osteoarthritis using the VAS score and KOOS index.

CONFLICT OF INTEREST

Every author stated that there are no conflicting interests in this research.

ACKNOWLEDGMENT

The authors would like to express gratitude for the lecturers and supervisor of our team, particularly dr. Ghana Adyaksa, M.Si.Med, Sp.OT and dr. Desy Armalina, M.Si.Med for the great advices.

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