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

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Abstract

Background: Osteoarthritis is an inflammatory joint disease that affects about 43 million people in the world with 80% of the geriatric population. Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) are usually used as pain relievers to reduce the symptoms of osteoarthritis. However, treatment with NSAIDs is considered to cause certain side effects, so the treatment solution using turmeric extract (*Curcuma longa*) can be used as a main treatment instead of NSAIDs with minimal side effects.
Objective: This systematic review and meta-analysis aimed to evaluate the efficacy and safety of curcuma extract in the treatment of geriatric patients with knee osteoarthritis.
Method: This systematic review and meta-analysis were made with a systematic literature search method from four databases, such as PubMed, ScienceDirect, and ProQuest. Inclusion criteria included experimental Randomized Control Trial (RCT) and discussed related topics. Results were shown as mean difference (MD) and standard deviation (SD). A fixed-effect model (FEM was used when the included studies were considered homogenous), which was indicated by an I^2 value of less than 40%. The risk of bias was assessed using the Cochrane risk-of-bias tool for randomized trials (RoB 2).
Result: This study included five randomized control trial studies with a total of 671 participants. VAS score declined with a significant pooled mean difference (MD) of -1.94 [95% CI : (-2.97) - (-0.92), P = 0.0002] with I^2 showing 99%. 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%.
Conclusion: Herbal extracts have better efficacy and safety than placebo and are comparable to the use of NSAID drugs through mechanisms such as anti-inflammatory and antioxidant with minimal side effects.
Keywords: *curcuma, osteoarthritis, geriatric*

Introduction

Osteoarthritis (OA) is the most common form of arthritis in the world with approximately 43 million people suffering from OA of which 80% are geriatric patients.[1] In 80% of OA patients experience knee pain, generally called knee osteoarthritis (KOA), which affects more than 300 million people around the world.[2] In 2011, there were nearly 1 million hospitalized patients with OA at approximately $15 billion, making OA the second highest medical cost disease.[3] According to data from *Riset Kesehatan Dasar* (Riskesdas) in 2018, the prevalence of joint diseases including OA in Indonesia in the population over 15 years old was 7.3% and the percentage of people over 55 years old was 53.15%.[4]

OA is an inflammatory disease commonly present with joint pain and loss of joint function that occurs through the interaction of multiple risk factors, mechanical stress, and abnormal joint movement resulting in articular cartilage changes that progress to surface fibrillation, cartilage irregularity, and focal erosion.[5] 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 activity that is often reported as a problem is using the toilet, walking up the stairs, and heavy housework.[6] Not only disrupted activities but also OA can impact mental issues like depressive disorders.[7] 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 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.[8] Long-term use of NSAID drugs will have side effects on the development of gastric mucosal injury and induced nephrotoxicity including electrolyte imbalance such as hyperkalemia.[9,10] Moreover, in the cardiovascular system, NSAIDs may be associated with increased blood pressure by 5 mmHg on average and risk of congestive heart failure.[10]

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. [11]

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.[12,13] The mechanism of treatment with turmeric (*Curcuma longa*) has the same goal as pharmacological treatment, namelyreducing 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.[14] This systematic review and meta-analysis aims to discuss the effectiveness and safety of providing treatment with natural ingredients compared to NSAID treatment in geriatric patients with osteoarthritis.

Material and Method

This systematic review was conducted based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline that can be accessed through (https://prisma-statement.org/)

Eligibility criteria

Outcome Measure

Outcome measures that are assessed in this systematic review and meta-analysis were pain score using Visual Analog Scale (VAS) and Knee Injury and Osteoarthritis Outcome Score (KOOS). Both scoring systems were used to measure the severity of pain in knee osteoarthritis quantitatively. VAS score was used to measure knee pain in osteoarthritis patients. It contains word descriptions ranging from 0-10 (using cm with "0" indicating "no pain" and "10" indicating "unbearable or severe pain." It was filled by the patient themself by marking the indicator no pain, mild pain, moderate pain, and severe pain.[15]

KOOS is a questionnaire to assess the outcome of knee injury by patients themself. KOOS contains 5 subscales that are scored separately: Pain consists of 9 items; Symptoms consist of 7 items;

Eligible criteria included in this study were original research articles or research reports using human study with randomized controlled trial design. Criteria for included studies were determined using PICO criteria shown in **Table 1**. The excluded studies were narrative review, systematic review, meta-analysis, non-comparative research, in silico studies, in vitro studies, in vivo studies, technical reports, editor responses, scientific posters, study protocol, and conference abstracts. Articles with unavailable full-text, non-English, and irrelevant topics were also excluded.

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)

Function in daily living consists of 17 items; Function in sport and recreation consists of 5 items; Quality of life consists of 4 items. Each item has 5 possible answer options from 0 (none) to 4 (extreme). Scores were transferred to a 0-100 scale with 0 representing severe knee problems and 100 representing no knee pain.[16]

Data Sources 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.

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)

Selection process

After searching keywords written in **Table 2,** we used article type filters on each database to exclude the non-RCT article. 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 study selection processes were recorded in the PRISMA flow chart.

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).

Study risk of bias assessment (Qualitative Synthesis)

Each study included in this study was assessed by three independent reviewers according to the Cochrane risk-of-bias tool for randomized trials (RoB 2) which can be accessed at (https://methods.cochrane.org/bias/resources/rob-2-revised-cochrane-risk-bias-tool-randomized-trials). The different decisions between reviewers were later discussed and resolved between reviewers.

Quantitative Data Synthesis (Meta-Analysis)

Mean Difference (MD) and Standard Deviation (SD) data were calculated in this review. A fixed-effect model (FEM) was used when the included studies were considered homogenous (low variability in studies' results or variation due to random error), which was indicated by an I^2 value of less than 40%. Otherwise, we used a random-effect model (REM). The pooled estimate was presented in a forest plot.

Result

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. This review included 5 studies to be in the systematic review and meta-analysis. Our study selection process is presented in the PRISMA diagram flow chart in **Figure 1**.

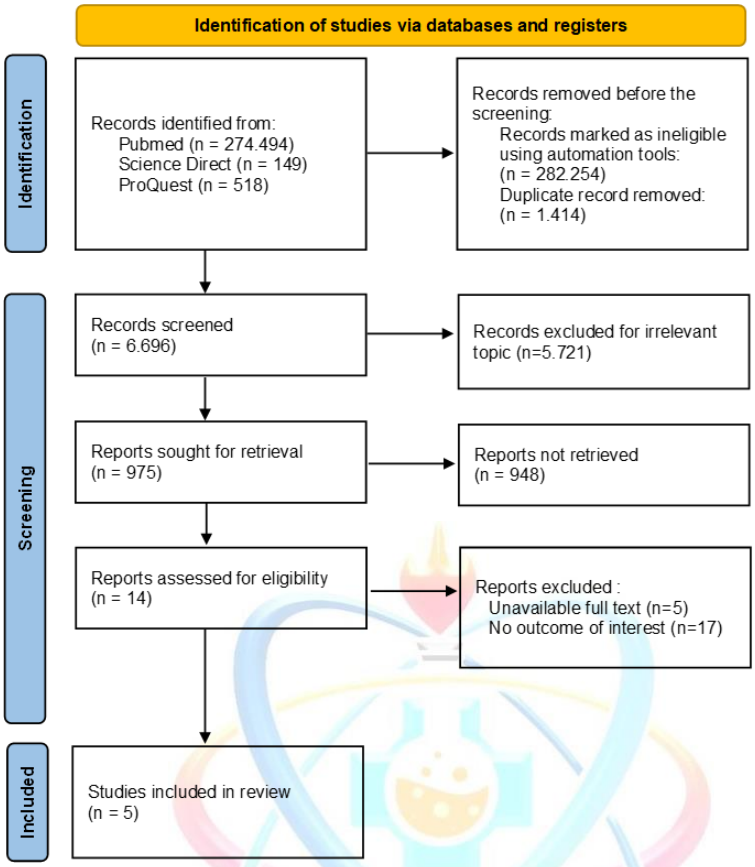

Figure 1. PRISMA 2020 Flow Diagram.

Study characteristics

From 5 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, conducted research on geriatric (> 60-year-old) patients. The rest of the included studies were approached 60 years of age for their participants.

Risk of bias in studies

The quality of each study was carefully analyzed by using the Cochrane risk-of-bias tool for randomized trials (RoB 2). 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 was summarized in **Figure**

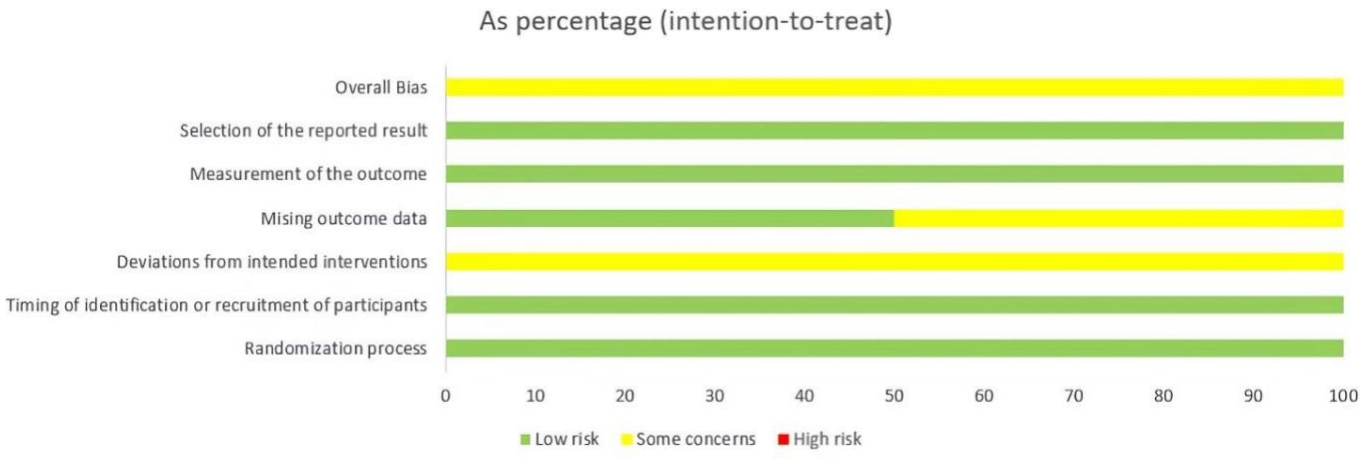

Figure 2. Risk of Bias Assessment Result

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					

Meta Analysis

Statistical analysis was performed using Review Manager (RevMan) v5.4 (Cochrane Collaboration, UK). Mean Difference (MD) and Standard Deviation (SD) with a Confidence Interval (CI) of 95% were then calculated in this review. 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 analyzed in this review.

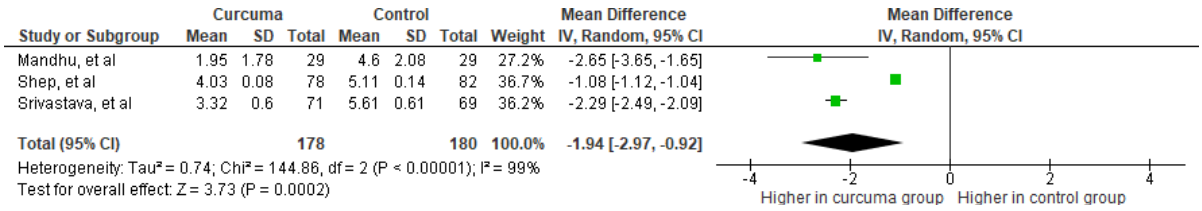

Figure 3. VAS Score

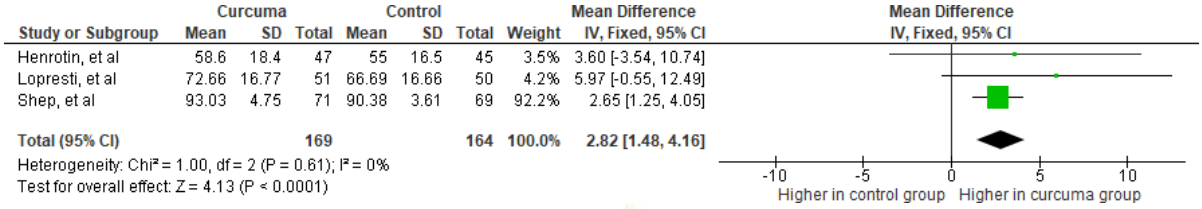

Figure 4. KOOS Index

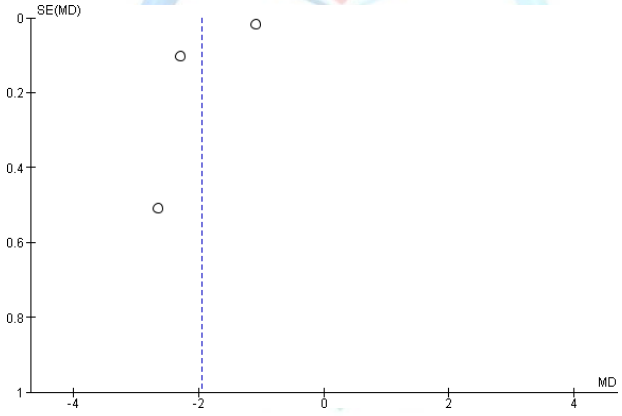

Figure 5. Funnel Plot of VAS Score

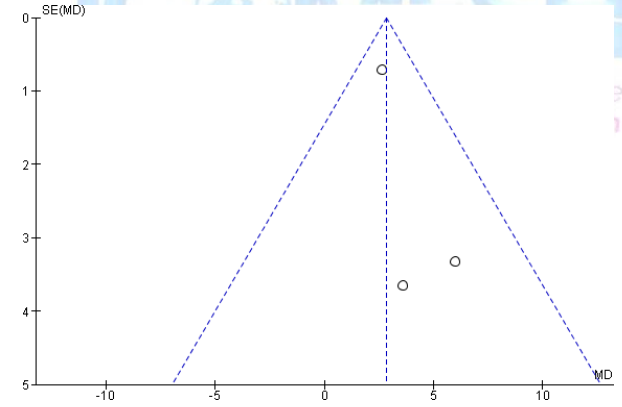

Figure 6. Funnel Plot of KOOS Index

Discussion

Curcuma Extract Improve Knee Pain on Knee Osteoarthritis

OA is an inflammatory disease with joint pain as the most common symptom with loss of joint function due to cartilage injury. The collagen matrix is damaged, causing chondrocytes to proliferate and form clusters of hypertrophic chondrocyte cells, leading to the growth of ossified cartilage and the formation of osteophytes.[5,21,22] This damage is associated with an increase in inflammatory cytokines in the form of TNF-α and IL-1β and matrix metalloproteinase (MMP). This will increase nitric oxide and Reactive Oxygen Species (ROS), resulting in increased oxidative stress which increases joint inflammation symptoms.[23] 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 ingredients of curcuma extract consist of many beneficial ingredients, such as phenolic pigments (including curcumin as a main ingredient that play a role as an anti-inflammation agent), essential oils (including cineole, linalool, α-terpinene, caryophyllene, ar-curcumene, zingiberen, curcumol, DL-turmerone, arturmerone, dehydrocurdione), campesterol, stigmasterol, β-sitosterol, cholesterol, fatty acids, and electrolyte elements potassium, sodium, magnesium, calcium, manganese, iron, copper, zinc, and other components.[24] 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.[14]

The combination of curcuma and other NSAID medication can improve better outcomes compared with NSAID alone. The studies aim to evaluate the efficacy of curcuma extract as an adjuvant therapy than NSAID alone for reducing OA-related pain. Seen from the VAS score data before and after treatment, the intervention group receiving a combination curcuma and NSAID has a lower VAS score after treatment than just giving the NSAID alone.[14,19]

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.[14,25] In some OA cases, 6.6% of patients treated with curcuma exhibited the least number of adverse effects during the intervention period.[17] As an adjuvant therapy, the addition of curcuminoid complex to diclofenac helps to reduce the GI side effects induced by diclofenac and reduces the requirement of H2 blockers.[18]

Curcuma extract as an alternative to NSAIDs in patients with osteoarthritis which mostly has adverse effects that are mild and transient.[18] In pharmacological terms, curcumin is a complete choleretic-cholagogue. The cleavage products of curcumin (ferulic and hydrofluoric acids) have cholecystokinin properties because they squeeze the gallbladder, while another principal product, paratholil methyl carbinol, has a strong choleretic activity. The choleretic effect of curcumin increases bile production by approximately 62%.[19] Although curcumin extract has adverse effects, there was no significant change in blood reports to complete blood count, kidney function, and liver function before and after the use of study medications. 20

Strengths and Limitations

This systematic review is the first systematic review and meta-analysis that focused on the efficacy of curcuma extract on geriatric patients with knee osteoarthritis. This systematic review assessed the curcuma therapy effects that were consumed orally to reduce osteoarthritis pain on samples in 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 not 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 recommend further randomized control trials with longer study duration to maximize the effect of curcuma extract with a larger sample size to be conducted to observe more about the efficacy and safety of curcuma extract therapy.

Conclusion

This systematic review and meta-analysis revealed that the use of curcuma extract is a prospective therapy for knee osteoarthritis in geriatric patients. 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

All authors declared there are no competing interests in this study.

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