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The The Efficacy of Herbal Extract on Osteoarthritis Treatment: A Meta-Analysis

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ABSTRACT

Osteoarthritis (OA) is characterized by pathology involving the entire joint, including cartilage degradation, osteophyte formation, and synovial inflammation, leading to pain, stiffness, and loss of normal joint function. Data on the incidence and prevalence of osteoarthritis in general, estimated at 302 million people worldwide. In indonesia there is an increase in cases of osteoarthritis in 2019 occurred by 153,2% in male population and 143,36% infemale population. This study aims to provide an evidence-based review of the efficacy of herbal extracts as an adjunctive or alternative therapy in the treatment of osteoarthritis. The search results were 746 studies, only 9 studies met the inclusion criteria. From the use of herbal extract combination of tamarindus indica and curcuma longa (turmeric), boswellia serrata, and zingiber officinale. The results obtained showed that the combination of curcuma longa (turmeric) and tamarindus indica showed a significant value which can be seen from the meta-analysis results of -9.72 (95% CI -15.52, -3.92) for the use of extracts for 5 days and -15.66 (95% CI -21.21, -10.11) for the use of extracts for 28-30 days, indicating that the combination of tamarindus indica and curcuma longa has potential as a long-term or short-term osteoarthritis therapy.

Keywords: osteoarthritis, boswellia serrata, zingiber officinale, tamarindus indica

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INTRODUCTION

Osteoarthritis (OA) is a disorder involving movable joints characterized by cell stress and extracellular matrix degeneration. The disease initially presents as a molecular disruptions, such abnormal joint tissue metabolism, which later progress to anatomical and physiologic changes. These change include cartilage degeneration, bone remodeling, osteophyte formation, joint inflammation and loss of normal joint function, potentially leading to significant health issues (Pepelyshev & Tsogtsaikhan, 2015).

Data on the incidence and prevalence of osteoarthritis in general, an estimated 302 million people worldwide, 10% of men and 18% of women aged 60 years and older have symptomatic osteoarthritis (Allen et al., 2022; Kolasinski et al., 2020). According to data from the Global Burden of Disease (GBD), the Age-Standardized Incidence Rate (ASIR) for OA increased by 0,32% annually worldwide, or almost 9% over a 28 year period (Wu et al., 2021). The Indonesian population has 5,5 million women and 4,1 million men suffering from osteoarthritis in 2019. The increase in osteoarthritis cases in 2019 occurred by 153,2% in male population and 143,36% in female population. This indicates that, in comparison to 1990, the number of osteoarthritis cases has more than doubled in 2019 (Butarbutar et al., 2024).

The American college of Rheumatology (ACR) guidelines, recommend therapies for the management of osteoarthritis (OA). Patients with hand, knee, and hip osteoarthritis (OA) are strongly advised to take oral NSAIDs as part of a conditionally approach to managing their

condition (Kolasinski et al., 2020). However, both selective and non-selective NSAIDs can have negative effects, though, such as renal damage, hypertension, and congestive heart failure. Non- selective NSAIDs are linked to higher risk of adverse events related to the upper gastrointestinal tract, whereas selective NSAIDs are linked to a higher risk of cardiovascular adverse events, such as myocardial infraction (Kan et al., 2019). NSAIDs should be used with caution in those with gastrointestinal disease including selective cox-2 inhibitors or non selective NSAIDs with the addition of a gastroretroprotective agent (Abramoff & Caldera, 2020).

It is crucial to look for alternate pain relief methods, to address the adverse effects of NSAIDs drug use (Luo et al., 2020). Boswellia, capsaicin, devil's claw, essential oils, feverfew, ginger, St.John's Wort, turmeric, valerian root, and willow bark are the most commonly reported herbs that relieve pain (Luo et al., 2020).

Tamarindus indica (tamarind) is a member of the sub-family *caesalpinioideae* and the plant family *fabaceae* (formerly known as *leguminoseae*) (Komakech et al., 2019). Tamarind contains 16-18% plant acids (including nicotinic acid-vitamin B3), along with volatile oil such as geranial,geraniol, and limonene. It also includes sugars, pectin, 0.8% potassium, and fats (Andrew chevallier, 2016). Numerous studies have documented anti-microbial, anti-viral, anti-venom, anti-diabetic, anti-asthmatic activity, anti-oxidant, anti-malarial, and anti-inflammatory properties in different portions of the tamarind tree (Ghaly et al., 2023).

Curcuma longa, commonly known as turmeric, is a perennial herbaceous plant from the *zingiberaceace* family (Andrew chevallier, 2016). *Curcuma longa* also has pharmacological actions that include anti-inflammatory, anti-tumor, antioxidant, lipid-regulating, and anti-coagulant properties (Benameur et al., 2023). Curcumin has anti-inflammatory and analgesic effect similar to those of NSAIDs for arthritis and has a lower incidence of adverse reaction, curcumin therapeutic affectiveness in treating arthritis has been tentatively verified by several clinical investigations (Atabaki et al., 2020).

NXT15906F6 also known as TamaFlex™ is a strandardized botanical composition that consists of an anaqueous ethanol extract of *cucuma longa* (turmeric) rhizome and aqueous ethanol and extracts of *tamarindus indica* seeds (Badmaev et al., 2018). *Curcuma longa* rhizome and *tamarindus indica* seeds are traditionally used in food applications. The polyphenolic proanthocyanidins found in tamarind seeds are abundant. These phytochemicals offer protection against oxidative stress and have anti-inflammatory properties (Sundaram et al., 2015). Curcuminoids are potent cyclooxygenase (COX-1 and COX-2) inhibitors, and they also reduce proinflammatory mediators including TNF- and IL-6 (Rahmani et al., 2018).

Boswellia serrata, belongin to *Burseraceae* family (Andrew chevallier, 2016). Boswellic acid, the main active ingredient of *Boswellia serrata* gum, is known to inhibit the 5-lipooxygenase (LOX) pathway, wich is the main source of pro-inflammatory leukotrienes (Kim et al., 2020) .Clinical research has demonstrated that *Boswellia serrata* extract not only has anti-inflammatory and anti-arthritis properties, but also physical function. Numerous clinical investigations have documented the effectiveness of Boswellia extract as possible anti-inflammatory medications for osteoarthritis (Yu et al., 2020).

Zingiber officinale (Ginger), which belongs to the *zingiberaceae* family (Mao et al., 2019). Ginger has active ingredients have antioxidant, anti-inflammatory, anti-diabetic, anti-viral, and anti-cancer (Al Hroob et al., 2018). Scientists are interested in zingiberaceae because they are dietary anti-inflammatory agents and because human pilot studies indicated benefits for chronic diseases including osteoarthritis, rheumatoid arthritis, and major depressive disorder (Lakhan et al., 2015). From this background, osteoarthritis is a considerable problem because there are side effects from the use of NSAIDs for osteoarthritis therapy. The use of

alternative drugs or additional drugs herbal extracts can help patients with osteoarthritis to make good choices from the use of drugs that have severe side effects. Therefore, we hope the results of this meta-analysis review will provide better evidence for the clinical application of herbal extracts in the treatment of Osteoarthritis.

METHOD

Literature screening and data extraction

The database search resulted in 746 studies that will be screened using the Preffered Reporting items for Systematic reviews and Meta-analysis (PRISMA 2020) flow diagram. As per figure 1, nine studies were included in this study. From the nine studies included in the review, data will be extracted in the form of title, author, country, publication time, sample size, comparators, outcome, and study design.

Search Strategy

Scopus, Cochrane library, PubMed, BMC, Science Direct, were comprehensively searched for relevant studies from 2014 to 2024, prioritizing articles penned in English and we used search phrases by combining subject words and free words, we only used words related to *Curcuma longa, Tamarindus indica, Boswellia serrata, Zingiber officinale*, and Osteoarthritis to achieve a high recall rate. The search terms included (curcuma OR curcuminoids OR *curcuma longa* OR turmeric) AND (tamarind OR tamarindus OR *tamarindus indica* OR *tamarindus indicas*) AND (osteoarthritis OR osteoarthritis knee OR hip osteoarthritis). (boswellic OR boswellia OR *boswellia sacra* OR *boswellia serrata* OR *boswellia carteri*) AND (osteoarthritis OR osteoarthritis knee OR osteoarthritis hip). (ginger OR zingiber OR *zingiber officinale*) AND (osteoarthritis OR osteoarthritis knee OR hip osteoarthritis)

Inclusion And Exclusion Criteria

Inclusion and exclusion criteria in the present study were based on the Population, Intervention, comparator and outcome (PICOS) structure.

1. Population : Patients with osteoarthritis
2. Intervention : Herbal extract
3. Comparator : Other treatment for OA, such as *placebo* or conventional medicine
4. Outcomes : Alleviating pain
5. Study design : Randomized Controlled Trials (RCTs)

The exclusion criteria were as follows : (1) repeated report (2) research data that could not be extracted, were incorrect, or were incomplete (3) animal research

Statistical Data Analysis

We performed statistical analysis using JASP statistical software to visualize the forest plot. For each included study, the meta-analysis with mean difference output required input data of the mean difference of changes in VAS scores over the duration of therapy, and the total sample size.

Bias Risk Assesment

We used the risk of bias assessment tool provided in the Cochrane risk-of-bias assessment tool for randomized trials (RoB 2). To evaluate possible bias in research studies by evaluating the methodological quality of the included RCTs. The evaluation content mainly includes the randomization process, deviations from the intended intervention (assignment

effects to the intervention), missing outcome data, measurement of outcomes, selection of reported outcomes. Each evaluation result can be judged as low risk, high risk, or some concerns.

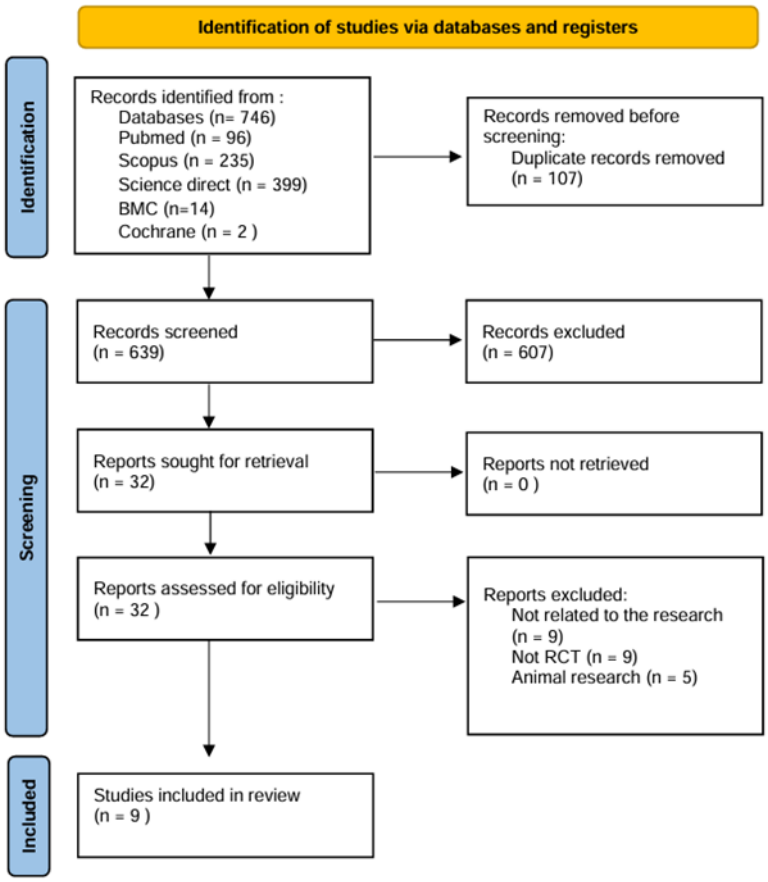

Figure 1. PRISMA

Table 1. Study Characteristics

No	Studies	Country	Patients	Interventions	Comparison	Outcome	Study design	Sample size
Boswellia serrata								
1.	Amalraj et al., 2019	India	OA, 40-75 years	250 mg of Acujoint™ (containing Boswellia serrata, Piper nigrum, kaempferia galanga, and Cureit™)	Combination of Glucosamine (1500mg) and Chondroitin (1200 mg)	VAS score after 30 days and 90 days of treatment	Randomized, double-blind, placebo-controlled trial	Total 24 Acujoint™ = 12 combination of Glucosamine and Chondroitin = 12
2.	Majeed et al., 2019	India	OA, 35-75 years	169,33 mg BSE (Boswellia serrata extract) tablets were	Placebo	VAS score after 120 days of	Randomized, double-blind, placebo-	Total = 48 BSE treatment = 24 Placebo = 24

No	Studies	Country	Patients	Interventions	Comparison	Outcome	Study design	Sample size
				given twice a day.		treatment	controlled trial	
3.	Karimifar et al., 2017	Iran	OA Knee, 40-80 years	Elaeagnus/Boswellia three times daily with meals for 4 weeks.	Ibuprofen	VAS score after 4 weeks of treatment	Randomized, double-blind, placebo-controlled trial	Total = 75 Elaeagnus/Boswellia = 26 Ibuprofen = 26
4.	Karlapudi et al., 2022	India	OA, ± 40 years	One 50 mg capsule of Aflapin b.i.d. (100 mg/d) (Aflapin b.i.d. composition from Boswellia serrata gum resin.)	Placebo	VAS score after 30 days of treatment	Randomized, double-blind, placebo-controlled trial	Total = 70 Aflapin b.i.d. = 35 Placebo = 35
5.	Bender et al., 2024	Central Europe (Budapest, Lakitelek, Kalocsa, Kakasszék)	Knee OA, mild to moderate 40-80 years	Received Loxacon® (*Boswellia serrata extract* 166 mg etc.)capsules for 5 weeks	Placebo	VAS score after 5 weeks and 5 weeks + 60 days of treatment	Randomized, double-blind, placebo-controlled trial	Total = 88 Loxacon caps = 28 Placebo = 30
Combination of *tamarindus indica* and *curcuma longa* (turmeric)								
6.	Prasad et al., 2023	India	OA, mild to moderate	NXT15906F6 (TamaFlex™) daily after breakfest	Placebo	VAS score after 5 days and 28 days of treatment	Randomized, double-blind, placebo-controlled trial	Total = 150 NXT15906F6 (TamaFlex™) = 50 Placebo = 50
7.	Kare et al., 2022	India	OA, 40-70 years	250 mg NXT15906F6 and 300 mg of NXT19185 daily for 56 days	Placebo	VAS score after 5 days and 30 days of	Randomized, double-blind, placebo-controlled trial	Total = 90 NXT15906F6 250 mg/day = 30 NXT19185 300 mg/day = 30 Placebo = 30

No	Studies	Country	Patients	Interventions	Comparison	Outcome	Study design	Sample size
						treatment		
Zingiber officinale								
8.	Afshar et al., 2022	Iran	OA, 40-85 years	30 ml G-Rup® syrup (combination of 150 mg/ml ginger extract and 100 mg/ml honey) twice every day for a 12 week period.	Placebo	VAS score after 6 weeks and 12 weeks of treatment	Randomized, double-blind, placebo-controlled trial	Total = 44 G-Rup® = 22 Placebo = 22
9.	Baek et al., 2024	Korea	OA, 50-80 years	1600 mg of GGE03 per day (as 2 tablets per day, containing 480 mg of steamed ginger extract)	Placebo	VAS score after 12 weeks of treatment	Randomized, double-blind, placebo-controlled trial	Total = 100 GGE03 = 50 Placebo = 50

RESULTS AND DISCUSSION

Boswellia Serrata

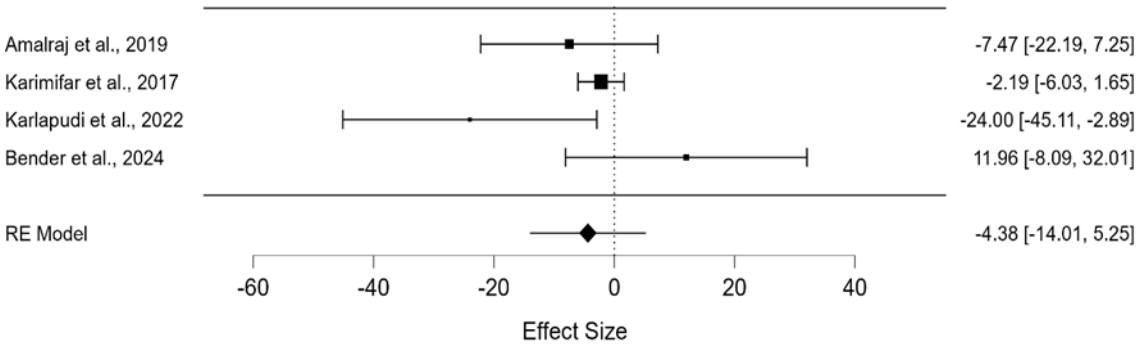

Figure 2. Forest Plot of Boswellia serrata use <10 week

There were four studies that could be meta-analyzed on Boswellia therapy for <10 weeks. In Research (Karlapudi et al., 2023) reported that in his study there was a decrease in VAS of -24.00 (95% CI -45.11, -2.89) this figure is statistically significant. While the other three studies (Amalraj et al., 2019; Bender et al., 2024; Karimifar et al., 2017) did not show statistically significant results. Study (Amalraj et al., 2019; Karimifar et al., 2017) reported that the use of Boswellia for <10 weeks can reduce VAS scores with a decrease in each study of (Amalraj et al., 2019) -7.47 (95% CI -22.19, 7.25) and study (Karimifar et al., 2017) -2.19 (95% CI -6.03, 1.65) respectively, but the (Bender et al., 2024) study reported the opposite, that the use of Boswellia for <10 weeks had no effect on reducing pain assessed by VAS scores with an increase of 11.96 (95% CI -8.09, 32.01).

It can be concluded that short-term Boswellia therapy for < 10 weeks, lowered the average VAS score by -4.38 (95% CI -14.01, 5.25), but this figure is not statistically significant, although this short-term Boswellia therapy is proven to reduce / reduce pain. Due to several factors, firstly because the number of studies is small, secondly the results are very diverse, there are studies that report a decrease in pain and there are studies that report no improvement in pain, and of the four studies that were meta-analyzed there was only one significant study.

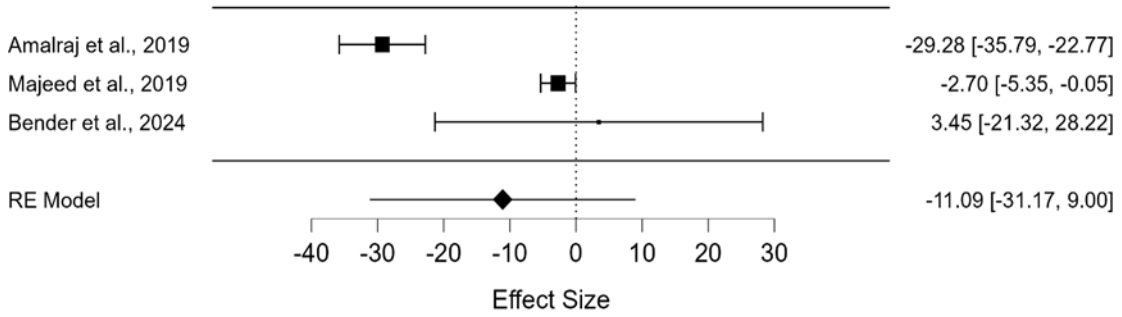

Figure 3. Forest Plot of Boswellia serrata use >10 week

There were three studies that could be meta-analyzed on Boswellia therapy for >10 weeks. Of the three studies, two were statistically significant, while one was not statistically significant. The study by (Amalraj et al., 2019) showed a significant reduction in VAS score of -29.28 (95% CI -35.79, -22.77). The study by (Majeed et al., 2019) also reported a decrease in VAS score of -2.70 (95% CI -5.35, -0.05), both studies were statistically significant. There is one study that is not statistically significant, the study by (Bender et al., 2024) where the study shows that boswellia therapy for >10 weeks does not reduce pain in osteoarthritis patients, which means that the study is not statistically significant with a value of 3.45 (95% CI -21.32, 28.22).

It can be concluded that long-term Boswellia therapy for >10 weeks reduced the average VAS score by -11.09 (95% CI -31.17, 9.00), but this figure is not statistically significant because the Convidence interval intersects the null line. Unfortunately the study by boswellia whether short-term or long-therm, although the results both lowered the average VAS score, either short-term or long-term therapy, but the results of the meta-analysis are both not statistically significant.

Combinaton of Tamarindus indica and Curcuma longa (turmeric)

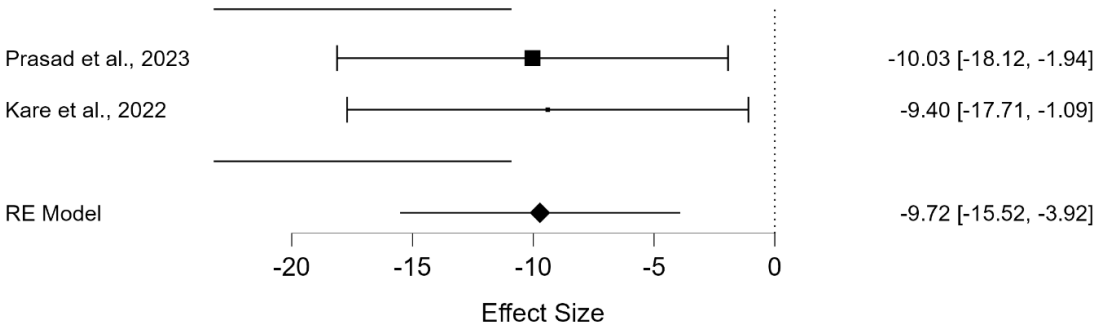

Figure 4. Forest Plot of combination Tamarindus indica and Curcuma longa use 5 days

There are two studies that can be meta-analyzed on the combination therapy of tamarindus indica and curcuma longa for five days. From the results of the meta-analysis, it was found that both studies showed a significant decrease in VAS scores, after administering a combination of tamarindus indica and curcuma longa in the short term for five days. The average decrease in VAS scores that occurred in each study was (Prasad et al., 2023) obtained a value of -10.03 (95% CI -18.12, -1.94) and study (Kare et al., 2022) obtained a value -9.40 (95% CI -17.71, -1.09) respectively.

It can be concluded that short-term tamarindus indica and curcuma longa combination therapy for five days reduced the average VAS score by -9.72 (95% CI -15.52, -3.92). Where this figure is statistically significant and this decrease shows that the combination of tamarindus indica and curcuma longa has potential as a short-term osteoarthritis therapy because it can reduce pain if taken even for only five days.

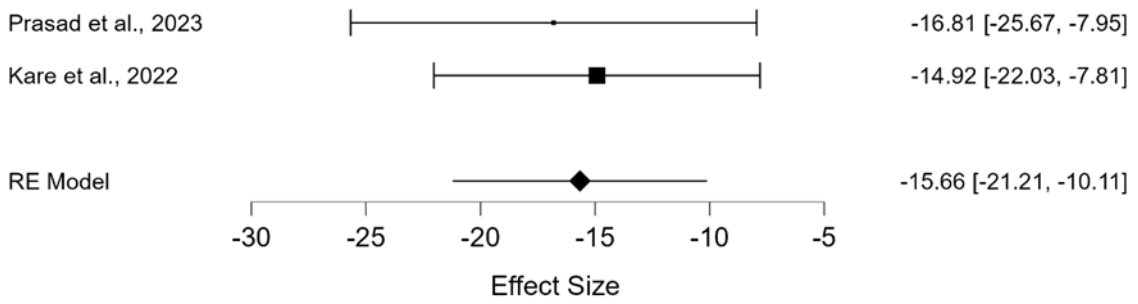

Figure 5. Forest Plot of combination Tamarindus indica and Curcuma longa use 28-30 days

There are two studies that can be meta-analyzed on the combination therapy of tamarindus indica and curcuma longa for twenty-eight to thirty days. Both studies showed a significant decrease in VAS scores after long-term administration of tamarindus indica and curcuma longa combination therapy, and also showed that there was a greater decrease in VAS scores than the combined score decrease of only 5 days. The average decrease in VAS scores that occurred in each study (Prasad et al., 2023) obtained a value of -16.81 (95% CI -25.67, -7.95) and (Kare et al., 2022) study obtained a value of -14.92 (95% CI -22.03, -7.81) respectively.

It can be concluded that long-term combination therapy of tamarindus indica and curcuma longa for twenty-eight to thirty days, reduced the average VAS score by -15.66 (95% CI -21.21, -10.11). This was statistically significant, indicating that the combination of tamarindus indica and curcuma longa has potential as a long-term or short-term osteoarthritis therapy.

Zingiber officinale

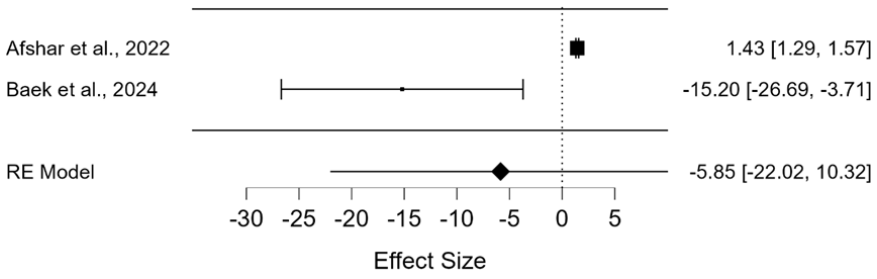

Figure 6. Forest Plot of Zingiber officinale use 12 week

There were two studies that could be meta-analyzed on zingiber officinale therapy for twelve weeks. The meta-analysis results of these studies showed opposite results. Research by (Baek et al., 2024) reported a decrease in VAS scores on zingiber officinale therapy for twelve weeks, but research by (Afshar et al., 2022) reported the opposite result, that in his study there was an increase or increase in VAS scores. The decrease in the average VAS score occurred in (Baek et al., 2024) study, which was -15.20 (95% CI -26.69, -3.71), while in (Afshar et al., 2022) study a value of 1.43 (95% CI 1.29, 1.57) was obtained that the use of zingiber officinale for twelve weeks had no effect on reducing pain assessed from the VAS score.

It can be concluded that zingiber officinale therapy for twelve weeks can reduce the average VAS score by -5.85 (95% CI -22.02, 10.32). However, this figure is not statistically significant due to the large difference between the two studies. Several other factors also played a role such as the small number of studies and each study showing very different results.

Risk of Bias

Table 2. Risk Of Bias

Studies	D1	D2	D3	D4	D5	Overall
Amalraj et al., 2019	+	+	+	+	+	+
Majeed et al., 2019	+	+	+	+	+	+
Karimifar et al., 2017	+	+	+	+	+	+
Karlapudi et al., 2022	+	+	+	+	+	+
Bender et al., 2024	+	+	+	+	+	+
Prasad et al., 2023	+	+	+	+	+	+

Studies	D1	D2	D3	D4	D5	Overall
Kare et al., 2022	+	+	+	+	+	+
Afshar et al., 2022	+	+	+	+	+	+
Baek et al., 2024	+	+	+	+	+	+

Domains :
D1 : Bias arising from the randomization process.
D2 : Bias due to deviations from the intended intervention.
D3 : Bias due to missing outcome data.
D4 : Bias in measurement of the outcome.
D5 : Bias in selection of the reported result.
Judgement :

High risk

Some concerns

Low risk

Overall, the methodological quality of 9 RCTs was acceptable, with the entire literature evaluation having low risk. The results of the literature quality evaluation of the 9 RCTs are shown in Table 2.

CONCLUSION

The results of this study indicate that the efficacy of using herbal extracts from boswellia serrata, a combination of tamarindus indica and curcuma longa (turmeric), and zingiber officinale there is a decrease in osteoarthritis VAS scores from each study,. The results of the meta-analysis showed that the use of herbal extracts from boswellia serata and zingiber officinale had insignificant results. While the combination of tamarindus indica and curcuma longa (turmeric) showed a significant value seen from the results of the meta-analysis of -9.72 (95% CI -15.52, -3.92) for the use of combined extracts for 5 days and -15.66 (95% CI -21.21, -10.11) for the use of combined extracts for 28-30 days, indicating that the combination of tamarindus indica and curcuma longa (turmeric) has potential as a long-term and short-term osteoarthritis therapy.

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