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Review Article

Effect of chamomile on musculoskeletal pain: A systematic review and meta-analysis of randomized controlled trials

Mostafa Ahmadi (MD, PhD) [1]
Seyyed Ali Mozaffarpur (MD, PhD) [1, 2]
Hoda Shirafkan (PhD) [1*]

1. Traditional Medicine and History of Medical Sciences Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, Iran
2. Department of Persian Medicine, School of Persian Medicine, Babol University of Medical Sciences, Babol, Iran

*** Correspondence:**
Hoda Shirafkan, Department of Social Medicine, School of Medicine, Babol University of Medical Sciences, Babol, Iran

E-mail: hodashirafkan@gmail.com
Tel: +98 1132194728

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Abstract

Background: Musculoskeletal pain is a common and bothersome condition influencing a large segment of the population. It can significantly impact individuals' quality of life and limit daily activities. Traditionally, chamomile (Matricaria chamomilla) has been used for its pain-relieving properties. This systematic review and meta-analysis aimed to investigate the efficacy of chamomile in reducing musculoskeletal pain.

Methods: We searched English language databases including Cochrane, Scopus, PubMed, Web of Science, and Google Scholar for published studies up to July 2024. Studies examining chamomile's influence on musculoskeletal discomfort in humans were included. In-vitro, animal, and observational studies were excluded.

Results: A total of eight studies were analyzed. The findings suggest a potential analgesic effect of chamomile compared to placebo. Additionally, no significant difference was found between chamomile and other pain medication. The studies included in this review, however, exhibited significant heterogeneity.

Conclusions: Chamomile may be a promising alternative for pain management due to its potential analgesic effect and lack of significant difference compared to other pain medication; however, more research is needed.

Keywords: Chamomile, VAS, Musculoskeletal pain, Clinical trial, Meta-analysis.

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Musculoskeletal pain is a usual and difficult issue that can be caused by physical activity, injury, or various diseases (1). These pains can significantly impact the quality of life of people and make it difficult to carry out routine activities (2). Musculoskeletal pains affect an important part of the population; the rate of involvement in these problems ranges from 13.5 to 47 percent (3). Musculoskeletal pain can be divided into acute (less than 3 months) and chronic (more than 3 months). Acute pain can usually be caused by disease or injury, while chronic pain is often associated with tissue-degrading processes.(4). Different causes can cause musculoskeletal pain: 1) Pain caused by activity usually occurs 24 to 72 hours after exercise. 2) Pain caused by musculoskeletal injury: This type of involvement can be caused by sprains, strains, and tears. 3) Pain caused by inflammatory diseases: This includes different types of arthritis. 4) other conditions: vitamin D deficiency, fibromyalgia, and carpal tunnel syndrome can also cause musculoskeletal pain (5).

Musculoskeletal pain presents with symptoms of pain, stiffness, swelling, muscle weakness, and fatigue (6). Depending on the pain-generating condition, various non-pharmacologic treatments such as exercise, physical therapy, rest, ice, massage, aroma, and oil therapy, or pharmacologic treatments such as NSAIDs, corticosteroids, and immunosuppressive drugs, or surgery are used (7-9). People are increasingly turning to natural approaches and alternative therapies to manage all types of pain, as well as musculoskeletal pain, one of which is the use of medicinal plants to reduce pain and inflammation (12-10).

Chamomile (Matricaria chamomilla) is an annual aromatic plant that grows naturally and spontaneously. This plant's white flowers are the part used as medicine. Chamomile contains compounds such as chamazulene and apigenin. chamazulene has anti-inflammatory and analgesic effects (13). Apigenin is an effective antioxidant and anti-inflammatory agent that can cause muscle relaxation and anti-anxiety effects (14). The active components of chamomile have antispasmodic and analgesic effects by blocking calcium channels (15). The antispasmodic effects of hydroalcoholic and oily extracts were investigated in an in vitro laboratory setting on human, pig, and mouse smooth muscles. The antispasmodic properties of chamomile were confirmed (16). Chamomile is significantly effective in treating pain caused by diseases such as migraine, dysmenorrhea, cesarean section pain, and gout (17-20).

Studies have shown that topical chamomile oil can reduce pain. In a study conducted on patients with osteoarthritis, it was found that the topical application of chamomile oil significantly reduced pain compared to a placebo (21). In addition, the use of chamomile oil in the treatment of carpal tunnel syndrome can reduce symptoms and improve functional conditions in patients with this disorder (22). Chamomile cream has shown its analgesic effects in treating the pain of pregnant mothers who underwent an episiotomy during childbirth (23). Due to the availability of chamomile all over the world, the many studies conducted on this plant, and the fact that no systematic review has been conducted on the effect of chamomile on reducing musculoskeletal pain, this review was conducted to investigate this issue.

Methods

Literature eligibility: In this systematic review, we assessed the studies on the effect of chamomile on musculoskeletal pain. Various clinical studies focusing on this impact were included in our review without any language restriction. We excluded all lab studies (including in-vivo and in-vitro studies), all types of review studies, book chapters, observational studies (case reports, case-control, cohort, and cross-sectional studies), and studies with low quality (based on RoB2 critical appraisal tool) from the study.

This research was approved by the Ethics Committee of Babol University of Medical Sciences with the ethics code IR.MUBABOL.HRI.REC.1401.205. We have registered our research in Prospero with code CRD42024588233. All experimental studies that included healthy individuals or those with musculoskeletal diseases of different ages, genders, and ethnicities who used various chamomile products with different doses were included in the study. In the experimental group, participants were administered chamomile in different dosages and forms, including oil, topical products, powder, tablets, or decoctions, or combined with other botanicals. The control group comprised individuals undergoing therapy with drugs or receiving a placebo, and healthy individuals who did not receive any treatment were included as participants.

Literature search and study selection: The English databases Cochrane, Scopus, PubMed, Web of Science, and Google Scholar, as well as the gray literature (conference papers) and references of the included articles, were evaluated up to July 2024. We also searched IRCT and Clinicaltrials.gov as clinical trial registry systems. Keywords obtained from the MeSH database and the free text method search were selected. The search strategy was formulated based on these keywords. Two researchers (MA and SAM) independently conducted searches in the titles and abstracts using the following search strategy: ((Musculoskeletal Pain) OR (Pain, Musculoskeletal) OR (Pains, Musculoskeletal) OR (Pain)) AND ((Chamomile) OR (Chamomiles) OR (Camomile) OR (Camomiles) OR (Camomiles) OR (Chamomile Oil) OR ("Chamomile Oil") OR (Chamomile Oils) OR (Oil, Chamomile) OR (Oils, Chamomile)). After removing duplicates, the articles were initially screened by two independent reviewers based on title and abstract (M.A. and S.A.M.). The full texts of the remaining studies were then assessed against the eligibility criteria. The references of the included articles were examined to find potentially related studies.

Data extraction: In the review process, two independent reviewers (M.A. and S.A.M.) extracted essential data from the studies using a consistent data extraction protocol. The reviewers knew the authors' names, institutions, and publication journals. Any discrepancies in data extraction between the first two reviewers were resolved by a third reviewer (H.Sh.). Subsequently, the extracted information was entered into an Excel sheet. The extracted data from each study is as follows: Author’s last name, publication year, implementation area, study design, the sample size in intervention and control groups, the dosage and duration of medication, mean or median age of the studied population, and the mean and standard deviation of study outcomes.

The primary outcome, including changes in pain, was assessed based on VAS and other pain assessment tools. To critically appraise and evaluate the risk of bias for the included studies, we used the revised Cochrane risk-of-bias tool for randomized trials (RoB-2) tool published by Cochrane (24). This tool examines the studies from five

aspects (randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result). In each part, the articles' quality was scored with words (high risk of bias, low risk of bias, or some concerns) to determine the degree of the study bias. Two independent researchers (M.A. and S.A.M.) used the RoB-2 tool to appraise studies critically, and studies deemed low quality by consensus were excluded from the study. In case of disagreement between the two researchers, the third researcher (H.Sh.) reviewed the study.

Data synthesis and statistical analysis: In the present study, all statistical analyses were performed using STATA Version 17 (STATA Corporation, College Station, TX). The effect of chamomile on pain was quantitatively estimated by calculating the mean difference in pain and the differences in standard deviations (SD) before and after the intervention in each group. The SD differences were calculated by

$$\sqrt{SD(base)^2 + SD(after)^2 - 2correlation \times SD(base) \times SD(after)}$$

in which the correlation of before and after intervention observations was considered 0.5. When a trial reports a continuous outcome as a median and a measure of dispersion, it is confidently converted to a mean and standard deviation under the normality assumption (17). We used the Der-Simonian and Laird random-effects model to pool the weighted effect of estimates across included trials. The inverse variance method was used to estimate trial weights. All p-values were two-sided, and the significance level was at < 0.05.

We categorized trials according to their control group. We combined placebo-controlled studies as well as studies in which the control group was drug therapy (e.g., ibuprofen, diclofenac, etc.). We included studies with three groups (chamomile, placebo, and usual care) in both sections. We examined funnel plots and conducted the Egger test and Begg's rank correlation test to evaluate the possibility of publication bias. If $p > 0.10$, it was considered no evidence of publication bias. Publication bias was further validated through a trim and fill analysis and associated forest plot.

We assessed heterogeneity using the I^2 statistic and visually inspecting the forest plots. I^2 values of 50% or more indicated substantial heterogeneity between studies, while I^2 values of less than 50% were considered to represent low heterogeneity. To evaluate the impact of each study on the overall results of the meta-analysis, we conducted a sensitivity analysis using the leave-one-out method. This involved repeatedly removing one study from the analysis and recalculating the overall effect size to see if it remained consistent. If the overall effect size did not change considerably, it indicated that the results were robust and not heavily influenced by any single study. However, if there was a considerable change, it suggested that the excluded study had a disproportionate impact on the overall results, possibly due to its size, quality, or methodological approach.

Results

Features of the included studies: During the database search, 631 articles were retrieved. After removing duplicates and non-trial articles, the titles and abstracts of 409 articles were screened. Nine studies, as depicted in figure 1, were ultimately included in the present review (25-33).

Based on table 1, there has been an increased focus on the impact of chamomile on controlling musculoskeletal pain in recent years. All studies were clinical trials. Two studies were conducted on muscle soreness patients, two studies on orthopedic and dental disorders, one study on rheumatoid arthritis individuals, one on knee osteoarthritis, and two studies on low back pain.

The sample size of the studies ranged from 20 to 74 participants, which were conducted in different age groups. Out of the nine studies identified, eight were carried out in Iran, and one in Syria. Among the articles, four studies examined the effect of the chamomile group against the control and placebo group, so various chamomile species products, such as capsules, decoction, powder, gel, and oil, were used in the intervention groups. A few studies had both a control group with a drug and a placebo group, so all of the studies used a placebo, and the four studies used standard treatment besides a placebo. The duration of assessment and follow-up in the studies varied from a minimum of 3 hours to 6 weeks, with chamomile doses administered one to three times daily. Among the nine articles, eight studies examined pain scores with VAS (Visual Analogue Scale) and one study examined pain with WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index).

Risk of bias assessment: Overall, the risk of bias was low in six studies, high in one study, and unclear in two studies. Eight studies reported randomization, and one did not. Of the nine studies, only one (27) had a high risk of bias and was excluded from the analysis (figure 2).

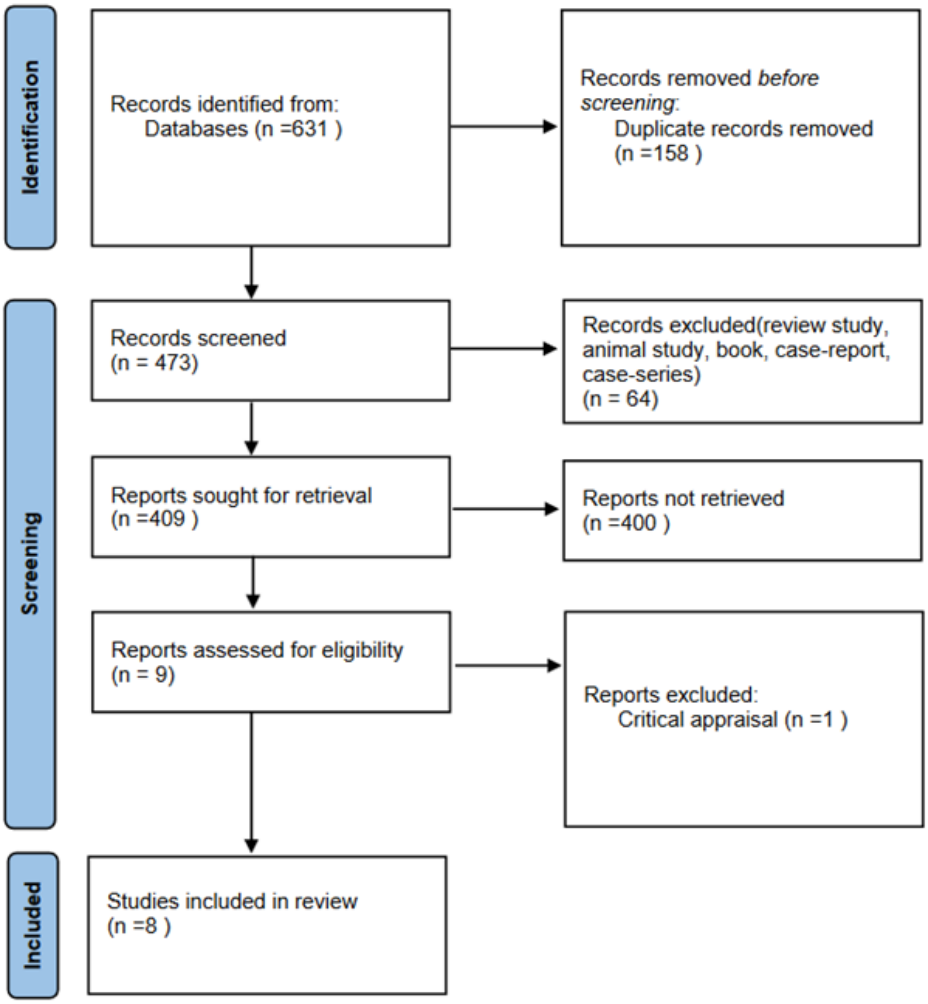

Figure 1. Study selection flowchart for inclusion in the systematic review

Table 1. Study characteristics of the included randomized clinical trials comparing the effect of chamomile to any other control groups

Author name (year)	Country	Type of disease	Age	Sample size	Tools of pain measurement	Intervention (dose of medication) Times per day duration	Duration and type of medication	Control (dose of medication) Times per day duration	Intervention result (before-after)	control result (before-after)
Shoara (2015) (25)	Iran	Knee osteoarthritis	38-65	56	WOMAC	topical chamomile oil 3times/day	3 weeks Topical	Diclofenac 3times/day	10.96±4.77 8.18±4.60	11.29±4.80 8.25±4.77
								paraffin 3times/day	10.96±4.77 8.18±4.60	11.32±4.20 9.68±5.50
Khatami (2017) (26)	Iran	muscle soreness	19-25	20	VAS	Chamomile extract (300 ml/D) daily	12days Oral	Chamomile essence and water (300 ml/D) daily	2.4 (0.84) 0.3 (0.48)	3.9 (0.99) 0.9 (0.73)
Pirouzpanah (2017) (27)	Iran	Rheumatoid arthritis	20-65	44	VAS	Chamomile tea (10 gr) 2 times	6 weeks Oral	wheat bran 2times	3.35±0.35 2.65±0.24	3.07±0.3 2.93±0.33

Author name (year)	Country	Type of disease	Age	Sample size	Tools of pain measurement	Intervention (dose of medication) Times per day duration	Duration and type of medication	Control (dose of medication) Times per day duration	Intervention result (before-after)	control result (before-after)
Saidi (2020) (28)	Iran	orthopedic surgery	15<	64	VAS	Chamomile (1 gr) 3 times	3 days Oral	black tea (1 gr) 3 times	7.53±0.19 5.93±0.20	7.31±0.13 5.68±0.17
								Melissa oficinalis (1 gr) 3 times	7.53±0.19 5.93±0.20	7.38±0.18 6.03±0.22
Naghavi -Azad (2020) (29)	Iran	muscle soreness	20-30	20	VAS	Chamomile Capsule (400 mg) 4 times	10 days Oral	Placebo (400 mg) 4 times	1.8 (1.12) 0.3 (0.5)	5.18 (0.44) 2.49 (0.51)
								Ibuprofen (400 mg) 4 times	1.8 (1.12) 0.3 (0.5)	3.19 (1.09) 2.89 (0.32)
Abolfazli (2021) (30)	Iran	Low Back Pain	25-60	74	VAS	Chamomile oil (5cc) 2 times	3 weeks Topical	sesame oil (5 ml) 2 times	5.05±2.09 3.00±1.98	5.13±1.79 3.27±2.00
Shirzad-Siboni (2022) (31)	Iran	low back pain	25-55	60	VAS	Chamomile oil (1.5cc) 3 times	3 weeks Topical	Paraffin oil (1.5 ml) 3 times	4.91±0.74 0.11±0.37	5.40±1.14 0.97±1.56
Rokbah (2023) (32)	Syria	third molar surgery	18-25	70	VAS	Chamomile gel (2ml)	3days Topical	Placebo gel (2ml)	3.20 (0.90) 1.77 (0.77)	4.26 (0.70) 3.06 (0.87)
Bahrami (2024) (33)	Iran	Preoperative Orthopedic	18<	60	VAS	Chamomile essence (3 drops/ hour)	3hour Inhalation	PEG 600 (3 drops/ hour)	7.13 (2.33) 5.33 (2.50)	6.60 (2.25) 6.23 (2.22)
								Damask Rose (3 drops/ hour)	7.13 (2.33) 5.33 (2.50)	6.57 (1.83) 4.67 (2.31)

VAS: Visual analogue scale, WOMAC: Western ontario and McMaster Universities Osteoarthritis index.

Effect of Chamomile on the pain compared to placebo: We divided the data into two parts to facilitate analyzing the meta-analysis results. Eight studies examined the effect of chamomile compared to placebo, which was dedicated to one part of the analysis. Four studies (25, 28, 29, 33) investigated the effect of chamomile compared to a drug, which comprised the second part of our analysis. In this meta-analysis, the effect of chamomile on reducing musculoskeletal pains compared to placebo was investigated in eight studies (25, 27-33). Results showed that chamomile had a greater effect on reducing pain compared to placebo (Hedge's g = -0.52, 95% CI: -0.95 to -0.08).

Alongside this, high heterogeneity was observed among the studies (I^2 = 80.37%), indicating significant differences in the results of different studies (figure 3). The funnel plot demonstrated significant asymmetry, which may indicate publication bias (figure 4). The result of Egger and Begg's test showed significant p-values. So, there was some concern about publication bias in a meta-analysis. We conducted a trim and fill analysis, and one study was added. After considering the imputed study, the pooled effect size was -0.627 (CI: -1.06, -0.19). Additionally, high heterogeneity was observed among the studies, suggesting substantial differences in the results of the various studies. Overall, the meta-analysis suggests a reduction in pain with chamomile. However, due to the potential publication bias and high heterogeneity, the interpretation of these results is subject to uncertainty. The leave-one-out analysis demonstrates that the results are generally robust and that removing any individual study does not significantly impact the overall result (figure 5). However, the Naghavi-Azad study (29) appears to have a slight influence on the overall results. When this study is removed, the 95% confidence interval of the overall effect moves closer to zero. Nevertheless, overall, the results of all studies are in the same direction, and all indicate a negative impact of chamomile on pain reduction.

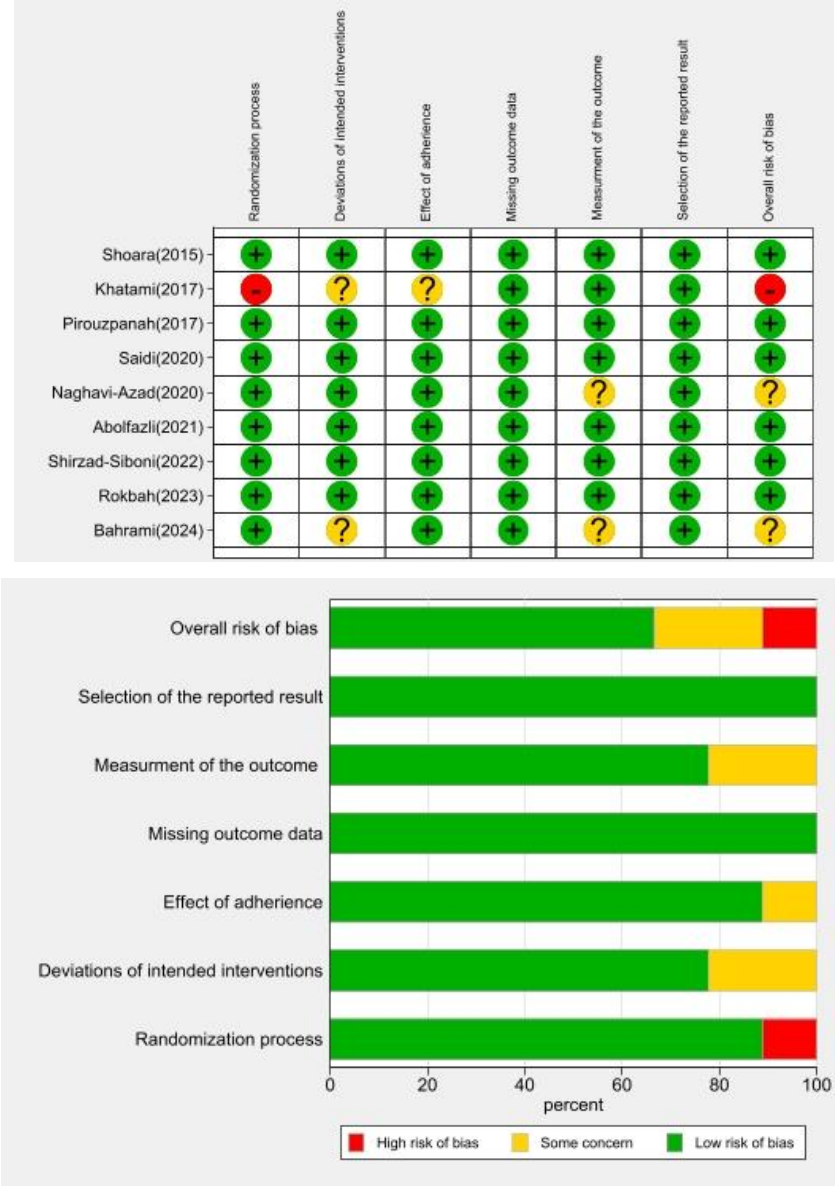

Figure 2. Risk of bias assessment of the included trials

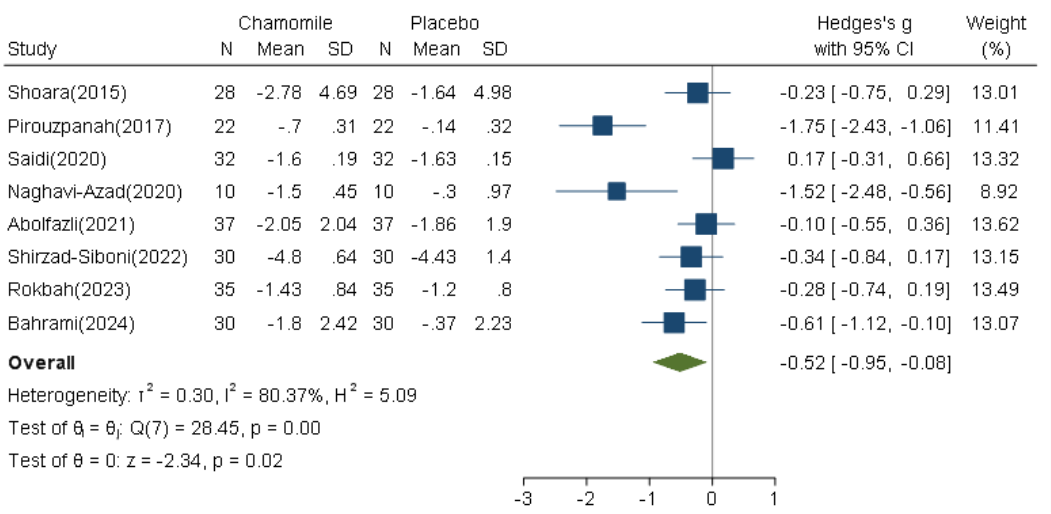

Figure 3. Forest plot of the effect of Chamomile on pain compared to placebo

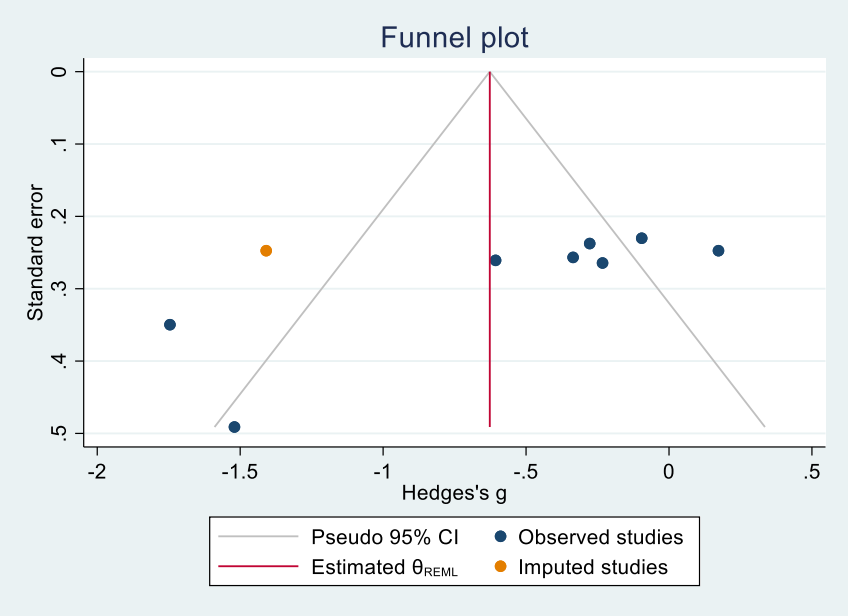

Figure 4. Funnel plot of chamomile-placebo studies and the result of trim and fill analysis. The imputed study is shown as an orange dot.

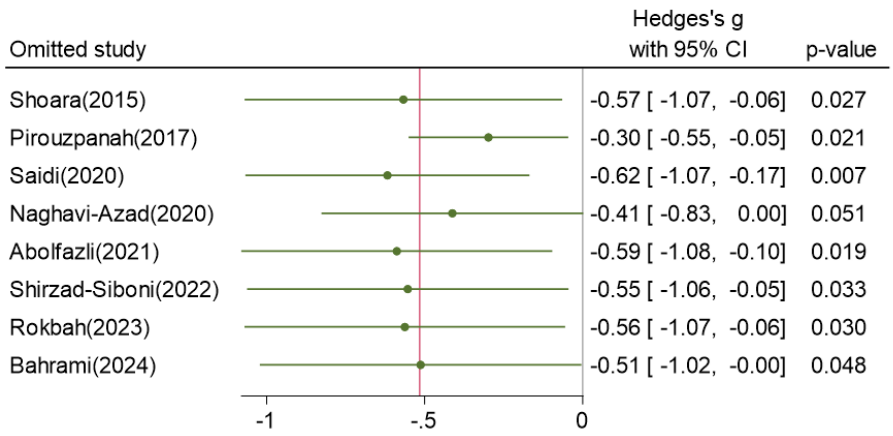

Figure 5. The forest plot of leave-one-out analysis for the effect of chamomile on pain compared to placebo

Effect of chamomile on musculoskeletal pain compared to other drugs: In this meta-analysis, the pain-relieving effects of chamomile were investigated in four studies (25, 28, 29, 33), compared to a control group. Pain reduction did not differ significantly between the chamomile and control groups (Hedge's g = 0.03, 95% CI: -1.03 to 1.09) (figure 6). However, there was very high heterogeneity among the studies (I^2 = 92.33%), indicating substantial differences in the results of the different studies. Potential causes of this heterogeneity may include differences in the study population, type of pain, and other factors related to the study design.

Despite the high heterogeneity, the overall effect of chamomile was not statistically significant. In this meta-analysis, funnel plot and trim and fill analysis (figure 7) were jointly used to assess the studies' homogeneity and detect potential publication bias. A slight asymmetry was observed in the funnel plot, suggesting the possibility of publication bias. However, Egger's and Begg's tests did not support this hypothesis. In this situation, trim and fill analysis did not confirm the existence of a study, and the pooled effect size after considering the imputed study was -0.388 (CI: -1.59, 0.81). Additionally, there is high heterogeneity among studies, indicating substantial differences in the results of different studies. Although chamomile demonstrated similar efficacy compared to other pain relievers, the results should be interpreted cautiously due to potential publication bias and high heterogeneity. Given that by excluding each study in the leave-one-out analysis, the overall effect size did not considerably change

(figure 8), it can be concluded that the results of our meta-analysis are relatively stable and not dependent on one or a few specific studies. The only research that appears to impact the results significantly is the Naghavi-Azad (2020) study. When this study is excluded, the 95% confidence interval of the overall effect moves towards zero. It approaches the boundary of statistical significance, indicating a better impact of chamomile compared to the drug. This suggests that this study may be somewhat influential in the overall results.

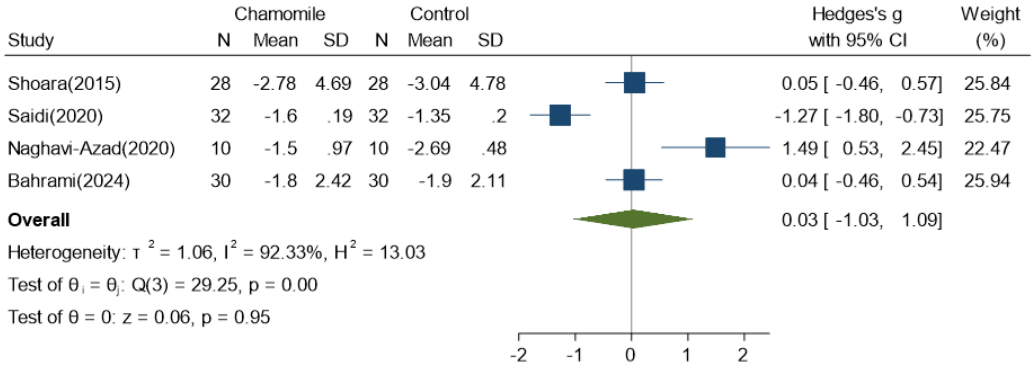

Figure 6. The forest plot of the effect of chamomile on pain compared to other drugs

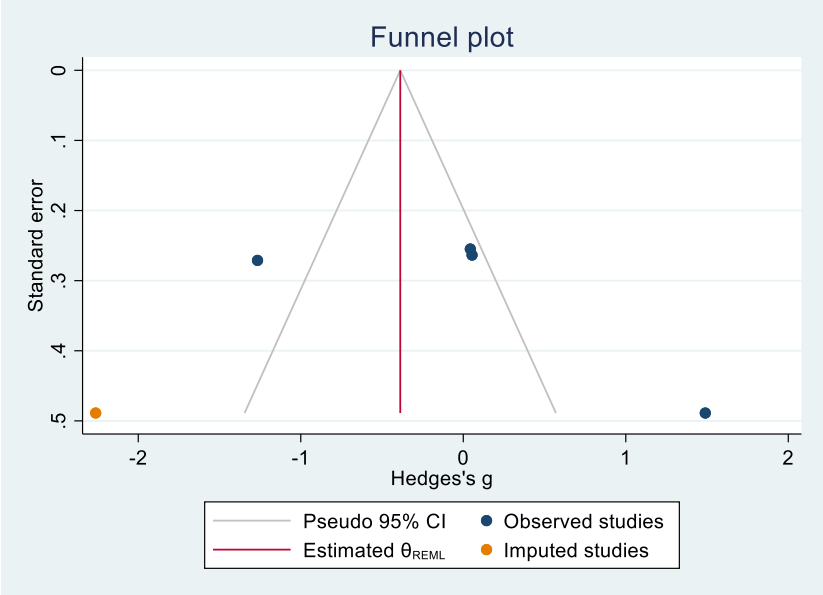

Figure 7. Funnel plot of chamomile-drug studies and the result of trim and fill analysis. The imputed study is shown as an orange dot.

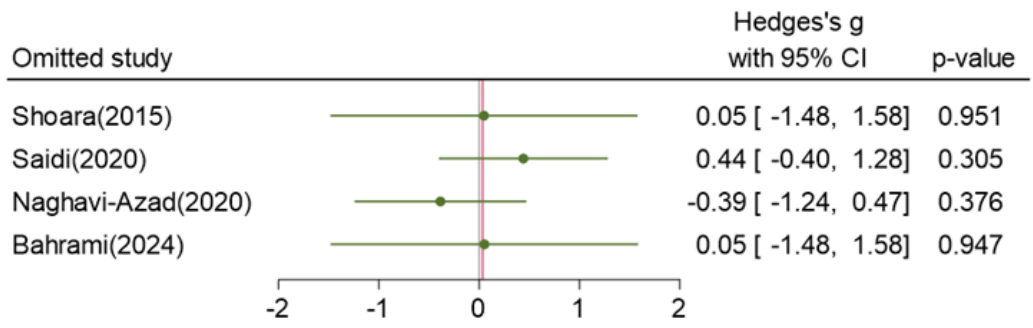

Figure 8. The forest plot of leave-one-out analysis for the effect of chamomile on pain compared to other drugs.

Discussions

In our systematic review and meta-analysis study, we investigated the potential of chamomile in various topical, oral, and aromatherapy forms to alleviate musculoskeletal pain. Chamomile has demonstrated efficacy in treating pain in different body regions, suggesting the possibility of generalizing its application to other types of pain. This issue has also been determined in other clinical trials, where chamomile can be used topically or orally to reduce pain in different organs and reduce pain in the involved organ (18, 34). The present meta-analysis aimed to elucidate the efficacy of chamomile in alleviating muscle pain. Our findings suggest a potential analgesic effect of chamomile when compared to placebo, which is consistent with previous findings suggesting chamomile's potential analgesic properties (35). However, the presence of substantial heterogeneity and potential publication bias necessitates a cautious interpretation of these results.

The observed heterogeneity underscores the complexity of the relationship between chamomile and pain reduction. Methodological variations across studies, including patient populations, pain types, chamomile dosages, and study designs, likely contributed to this heterogeneity. Moreover, the asymmetry in the funnel plot suggests the possibility of publication bias, where studies with null or negative findings might be underrepresented. These methodological limitations underscore the need for further research to clarify the analgesic properties of chamomile. Direct comparison of chamomile with standard painkillers yielded non-significant results and it was found that chamomile can be effective in reducing pain like standard medicine. In Linde's review article, it was stated that chamomile can be tested and effective in the treatment of musculoskeletal diseases such as rheumatoid arthritis and osteoarthritis compared to standard drugs (36). But the high level of heterogeneity prevented a definitive conclusion. The lack of a clear treatment effect in this analysis may be attributed to factors such as the heterogeneity of study designs, the choice of comparator drugs, or the specific pain conditions examined.

It appears that chamomile, with its various compounds, can exhibit analgesic and calming properties. This effect can be attributed to the compounds chamazulene and apigenin (14). Chamomile has been effective in reducing colic in infants and decreasing smooth muscle spasms in both animal and human models (16). The analgesic and vasodilatory effects of chamomile, along with its ability to reduce muscle spasms, may be due to the blocking of calcium channels in muscles and the increase of circulating nitric oxide (15). Other mechanisms through which chamomile can induce relaxation, tissue release, and pain reduction include the opening of potassium channels and its action on acetylcholine receptors (37). Chamomile, while effective in reducing pain in patients with musculoskeletal disorders, has also been shown to alleviate pain in various other conditions. In ailments such as migraines, post-cesarean pain, dysmenorrhea, and gout, chamomile has been utilized as an analgesic (17-20). Sensitivity analysis using omitted forest plots revealed that the results were generally robust to the exclusion of individual studies, except for the Naghavi-Azad study. This study's influence on the overall effect size, particularly in the chamomile-drug comparison, warrants further investigation.

Limitations: First, because of the few studies that were included, we could not perform a subgroup analysis, and different dosages of chamomile were used, so we could not assess the precise effect of the chamomile. Second, due to the high heterogeneity of the included studies, the meta-analysis's result was not conclusive. Third, there is a lack of access to all scientific databases for a more comprehensive search. Another limitation of the study was that assembling a heterogeneous patient population in terms of age, different causes of pain, and different severity of diseases limited the ability to conduct subgroup analysis.

Future prospective: Future research should address methodological limitations, investigate optimal doses of chamomile, and investigate specific pain conditions to elucidate the clinical relevance of chamomile as an analgesic agent. Further RCTs are needed to investigate the effects of chamomile on pain. Moreover, the duration of clinical studies should be extended. While the current meta-analysis provides preliminary evidence that chamomile has an analgesic effect compared to placebo and even indicates that chamomile can be as effective as other analgesics in reducing pain, considerable heterogeneity and possible publication bias limit the strength of these findings.

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Ethics approval: This research was approved by the ethics committee of Babol University of Medical Sciences with the ethics code IR.MUBABOL.HRI.REC.1401.205. We have registered our research in Prospero with code CRD42024588233.

Conflict of interest: There is no conflict of interest.

Author contribution: Mostafa Ahmadi: Data curation; investigation; methodology; writing – original draft; writing–review and editing. Seyyed Ali Mozaffarpur: Data curation; investigation; writing – review and editing. Hoda Shirafkan: Formal analysis; methodology; writing – review and editing.

Data availability: Data sharing does not apply to this article.

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